Universidade de Lisboa

Faculdade de Medicina

Instituto Politécnico de Lisboa

Escola Superior de Tecnologia da Saúde de Lisboa

Frailty and nutritional status in patients with neurodegenerative disorders

Diana Filipa Santos Miranda

Orientador: Prof. Doutor Joaquim José Coutinho Ferreira

Coorientador: Dra. Vânia Cristina Almeida Costa

Dissertação especialmente elaborada para obtenção do grau de Mestre em Nutrição Clínica

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Resumo

Introdução: A fragilidade é uma síndrome geriátrica que resulta do declínio de múltiplos sistemas fisiológicos associado ao processo de envelhecimento. Este declínio manifesta-se como um estado de vulnerabilidade aumentada a *outcomes* de saúde adversos, sendo considerado um forte preditor de incapacidade, dependência, institucionalização e morte. A malnutrição tem sido descrita como um fator de risco independente para o desenvolvimento da fragilidade.

Objetivos: O objetivo principal do estudo foi descrever a frequência da fragilidade em utentes institucionalizados com doenças neurodegenerativas no momento da admissão numa instituição de saúde. Os objetivos secundários foram descrever a frequência da desnutrição e avaliar a correlação entre a fragilidade e o estado nutricional. Adicionalmente, comparar a frequência da fragilidade e da desnutrição um e três meses após a admissão na instituição.

Métodos: Foi realizado um estudo piloto transversal e observacional. Todos os utentes admitidos no Campus Neurológico Sénior com idade ≥ 65 anos e com pelo menos uma doença neurodegenerativa foram incluídos. Foram estabelecidos três momentos de avaliação: admissão, um e três meses após a admissão. Em cada momento foi realizada uma avaliação do estado nutricional, através do *Mini Nutritional Assessment* (MNA), medidas antropométricas e da *Edinburgh Feeding Evaluation in Dementia Questionnaire* (EdFEQ-Q), e uma avaliação da fragilidade, através da *Marigliano-Cacciafesta Polypathological Scale* (MCPS).

Resultados: Foram incluídos 76 participantes com uma média de idades de 76±6.8 anos. As síndromes parkinsónicas foram as doenças neurodegenerativas mais frequentes na amostra (82.9%). A frequência da fragilidade foi de 71.1%, sendo que os utentes com síndromes parkinsónicas atípicas apresentaram uma frequência superior à dos utentes com doença de Parkinson (85.7 e 60%, respetivamente). Nos utentes com demência, a frequência da fragilidade foi de 69.3%. A frequência da desnutrição e do risco de desnutrição foi de 73.7%. A desnutrição foi mais frequente nos utentes com demência, seguidos pelas síndromes parkinsónicas atípicas e pelos doentes de Parkinson (30.8, 21.2 e 10%, respetivamente). Foram verificadas correlações estatisticamente significativas entre todos os parâmetros nutricionais e a MCPS, destacando-se o MNA e a EdFEQ-Q. Relativamente à fragilidade, não foram encontradas diferenças estatisticamente significativas entre os três momentos de avaliação. Verificou-se uma melhoria significativa do estado nutricional (MNA) apenas no grupo das síndromes parkinsónicas da admissão para o primeiro momento de reavaliação.

Conclusões: A prevalência da fragilidade em utentes institucionalizados com doenças neurodegenerativas é elevada, bem como a prevalência da desnutrição. A fragilidade e os parâmetros de estado nutricional apresentam correlações significativas.

Palavras-chave: Fragilidade; Doenças neurodegenerativas; Estado nutricional; Parkinsonismo; Demência

Abstract

Introduction: Frailty is a geriatric syndrome defined as a state of increased vulnerability to negative health outcomes that is considered the most powerful predictor of disability, dependence, institutionalization and death, and so considered a major health burden. Malnutrition has been described to be independently associated with frailty.

Objectives: Primary objective was to describe the frequency of frailty in institutionalized patients with neurodegenerative disorders in the moment of admission. Secondary objectives were to describe the frequency of undernutrition and to evaluate the correlation between frailty and nutritional status in the moment of admission. Additionally, to compare the frequency of frailty and undernutrition one and three months after admission.

Methods: A cross-sectional observational pilot study was performed. All patients aged 65 years and older with at least one neurodegenerative disorder admitted in Campus Neurológico Sénior were included. Three assessment moments were established: admission, one and three-months after. In each moment a nutritional assessment, through the Mini Nutritional Assessment (MNA), anthropometric measurements and the Edinburgh Feeding Evaluation in Dementia Questionnaire (EdFED-Q), and a frailty assessment, through the Marigliano-Cacciafesta Polypathological Scale, were conducted.

Results: 76 participants were included with a mean age of 76±6.8 years. Parkinsonian syndromes represented 82.9% of the sample. The frequency of frailty was 71.1%. Patients with atypical parkinsonism were significantly frailer than patients with Parkinson's disease (PD) (85.7 and 60%, respectively). 69.3% of the patients with dementia were frail. The frequency of undernutrition (and risk of) was 73.7%. Although not statistically significant, undernutrition was more frequent in dementia syndromes, followed by atypical parkinsonism and PD (30.8, 21.2 and 10%, respectively). Significant correlations were found between all the nutritional assessment parameters and the MCPS, being the strongest with the MNA and the EdFED-Q. In the one and three-months reassessment moments, statistically significant differences since the admission regarding the MCPS were not found. Statistically significant improvement in nutritional status since the admission was found only in the parkinsonian syndrome group one-month after the admission.

Conclusions: The prevalence of frailty in institutionalized patients with neurodegenerative disorders is high, along with the prevalence of undernutrition. Frailty and nutritional status parameters share significant correlations.

Keywords: Frailty; Neurodegenerative disorders; Nutritional status; Parkinsonism; Dementia

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List of Abbreviations

AA - Amino acids
AD - Alzheimer's disease
ADL - Activities of daily living
ALS - Amyotrophic lateral sclerosis
BMI - Body mass index
CBD - Corticobasal Degeneration
CC - Calf circumference
CDC - Center for Disease Control and Prevention
CDR - Clinical dementia rating scale
CES-D - Center for Epidemiological Studies depression scale
CFS - Clinical frailty scale
CI - Cognitive impairment
CNS - Campus Neurológico Sénior
COPD - Chronic obstructive pulmonary disease
CRD - Chronic respiratory diseases
CRF - Case report form
EdFED-Q - Edinburgh Feeding Evaluation in Dementia Questionnaire
ESPEN - European Society for Parenteral and Enteral Nutrition
FFMI - Fat-free mass index
FI - Frailty index
FMUL - Faculty of Medicine, University of Lisbon
FTD - Frontotemporal dementia
H&Y - Hoehn and Yahr scale
LBD - Lewy body dementia
LSHT - Lisbon School of Health Technology, Instituto Politécnico de Lisboa
MAC - Mid-arm circumference
MCPS- Marigliano-Cacciafesta Polypathological scale
MD - Mediterranean diet
MMSE - Mini mental state examination
MNA - Mini Nutritional Assessment
MSA - Multiple System Atrophy
MUST - Malnutrition Universal Screening Tool
ONS - Oral nutritional supplements
PD - Parkinson's disease
PFP - Physical frailty phenotype
PSP - Progressive Supranuclear Palsy
RCTs - Randomized-controlled trials
SGA - Subjective Global Assessment
VD - Vascular dementia
VP - Vascular Parkinsonism

Introduction

Frailty syndrome – Definition and concept

The older population is rapidly increasing worldwide, being expected 2000 million aged over 60 years by the year 2050[1]. This represents a challenge for societies and healthcare systems (especially long-term and social care), mainly due to the emerging need to guarantee the health and social-contribution capacity of elders to society, as well as to prevent the increased costs of an ageing population[1].

The concept of frailty has evolved since 1988, when being "frail" was synonymous of having more than 65 years, dependent on others for activities of daily living (ADL) and, frequently, institutionalized (easily confused with functional dependence)[2]. Definitions also evolved since then, and in the last 20 years the concept of frailty and its preventability potential grew in popularity in scientific communities[1,3]. In fact, frailty is a long-established clinical expression regarding the outlook and vulnerability of an individual[4].

Frailty is a common geriatric syndrome that results mostly from the cumulative decline of multiple physiological systems and their reserves associated with the ageing process[4–9]. This progressive and cumulative decline manifests itself as a state of increased vulnerability to negative outcomes when facing a stress event (whether is endo or exogenous), due to the low ability to regain homeostasis and functional abilities[4,7,9–12].

As described by Clegg et al., an apparently insignificant stress event, such as an urinary tract infection or the introduction of a new drug, can result in a striking and disproportionate response in frail elders[4]. This response may manifest as abrupt changes of functional state (mobility to immobility, postural stability to instability and risk of falls, functional independence to dependence) and in the mental state (lucid to delirious, confusion, and mental fluctuations)[1,4].

Since frailty is a process that develops over time, Fried et al suggested that it can be divided in stages, from robust to end-stage frailty, with different clinical presentations, and thus different potential for prevention or treatment (table 1)[9].

Stage of frailty	Characteristics
Robust	Resilient Rapid recovery from stress events
Subclinical frailty	Resilience appearance Slowly or incomplete recovery from stress events Possibility of adverse consequences
Early frailty	Clinical frail appearance Low tolerance to stress events No disability
Late frailty	Frail appearance Low tolerance to stress events and very slow recovery Disability due to decreased energy and/or strength
End-stage frailty	Severely frail appearance Weight loss and weakness Dependence and high risk of death within 12 months

Table 1. Stages of frailty progression (adapted from Fried et al[9]).

Frequent clinical symptoms of frailty are extreme fatigue, unintended weight loss, frequent infections, slow gait, muscle weakness and low energy expenditure[1,4,10]. Balance and gait impairments are considered major features of frailty and risk factors for falls[4,13]. In more severe frail stages, spontaneous falls occur due to impairment of postural systems such as vision, balance and strength[1,4]. The major concern with spontaneous falls is that, in addition to the significant decrease in mobility, often they repeat overtime and are strongly associated with fear of falling (psychological response), and reduced physical activity[4].

Fluctuating confusion, delirium, and impaired awareness are related to frailty due to reduced brain function integrity[4]. These symptoms, frequent in hospitalized and long-term care elders, may occur as outcomes of frailty after a stress event[4,14,15]. Another fluctuating sign of frailty is disability in patients that fluctuate between days with functional independence and days with significant dependence[4].

Frailty is considered the most powerful and strong predictor of disability and poor health outcomes such as falls, delirium, dependence, hospitalization, institutionalization and death, and so considered a major health burden[11,12,16].

Disability and comorbidity can coexist with frailty, although these concepts are not synonymous[10,17]. Disability is defined as the difficulty or dependency in ADL regarding selfcare or housekeeping and can occur as a consequence of an acute event such as hip fracture or stroke, which on this case makes it a risk factor for frailty[18]. Physical disability is frequent in the elderly population (20-30%) and tends to increase over ageing[18]. In late life, disability is mostly an outcome of diseases (comorbidity), physiologic alterations of ageing and frailty[18].

On the other hand, comorbidity refers to the concurrent presence of two or more diseases[18]. Is an independent risk factor, along with frailty, for disability, but also a contributor to the development of frailty[18].

Epidemiology

Frailty prevalence increases with age[1,4,19]. Worldwide, is estimated that in elderly population aged over 65 years the prevalence of frailty is 7%, while in elderly aged over 80 years it increases to 20%[8]. In general population, 5 to 27% are estimated to be frail and 35 to 51% are supposedly in pre-frail stages[8]. In Japan, the country with the highest life expectancy, the general prevalence of frailty is estimated to be 7% and in elders over 85 years old is 35%[20].

In health care institutions, such as nursing homes, the prevalence of frailty is expected to be higher, since institutionalization is one of the negative health outcomes of frailty[21]. Also, dependency, comorbidities, and malnutrition are frequent in this population[21–23]. Although few studies on this issue had been conducted, and despite the heterogeneous results, is estimated that frailty affects nearly half of the residents[21].

It is hypothesized that the accumulation of declines, that happens on frailty, starts its development earlier than old age, being influenced by health behaviours, health experiences, health exposures, and health events[1]. Also, the greater predisposition to decline results from a cumulative balance between risk and protective behaviours, experiences, and exposures[1]. From this point of view, acting to prevent frailty must be a continuous trajectory that starts early in life[1].

Physiopathology of frailty

The physiopathology of frailty is a complex multifactorial process that involves the decline on many physiological systems that collectively increase vulnerability to, apparently small, health status changes and/or minor stress events that include minor infections and surgeries, and the introduction of a new medication[1,4]. The stress event, as small as it can seem, can result in a sudden and disproportionate change in global health status such as from independent to dependent or from lucid to delirious[4].

Is generally accepted that frailty is a dynamic process, whose natural course is deteriorating over the ageing process (a major and irreversible contributor to frailty development)[1,4,12]. The ageing process *per se* is accompanied by changes in sensory abilities (such as hearing and vision), sleeping disorders, and urinary dysfunction, that can lead to social isolation, falls and poor quality of life[1].

The best studied body components related to frailty development and ageing are the brain, endocrine and immune systems, and skeletal muscle, that are intrinsically inter-related[4]. Additionally to other physiological systems, such as respiratory or cardiovascular systems, also nutritional status is believed to be strongly associated with frailty[4].

The brain suffers structural and physiological changes while ageing[4,24]. This changes are most evident on the hippocampus, which seems to be a key component on the development of cognitive decline and dementia[4]. Observational studies have been supporting an independent association between frailty and dementia[4,25,26]. Cognitive impairment (CI) can lead to nutritional problems, behaviour changes and falls, becoming an important component to assess regarding frailty[1,27–29].

Also, depression in elderly may be underdiagnosed and is strongly associated with frailty[1]. This condition, malnutrition and physical inactivity are potentially treatable contributor factors for frailty[1].

With ageing, the immune system tends to fail on to properly respond to acute inflammation. Inflammation highly contributes to increase the energy requirements and catabolism of skeletal muscle and fat mass, leading to anorexia, weight loss, weakness and undernutrition – characteristics of frailty[4].

Elderly patients are more vulnerable to malnutrition compared to general population[1]. Many factors contribute to this increased risk, including oral and dental health problems, reduced appetite, CI, impaired functional ability, and depression[1]. Weight loss and undernutrition are strongly associated with frailty, but unfortunately often underdiagnosed[1]. Sarcopenia is believed to be a major contributor, since it represents the progressive loss of muscle mass and strength associated with ageing[16]. The prevalence of sarcopenia can reach up to 50% in the elderly and, not surprisingly, usually it anticipates frailty[16,30]. Changes in the endocrine, immune and brain systems can affect the development of sarcopenia, that is also associated with physical inactivity and inadequate nutrition[4].

Although frailty is not synonymous of comorbidity, many frail elderly experience multiple chronic conditions such as diabetes, chronic renal failure, and osteoporosis, as well as neurodegenerative disorders[1,31]. Along with comorbidity, frail elderly often have multiple medications prescribed by different health providers with associated risks of drug interactions and adverse side effects[1,31]. More than 50% of older adults have a concomitant intake of five or more drugs (polypharmacy)[31–33].

Drugs may be seen as potential contributors to frailty[31]. In fact, polypharmacy is associated with increased risk of frailty in older adults not only due to the obvious increase of comorbidity with ageing, but also due to the overuse of, sometimes, unnecessary medication prescribed by several prescribors[31–33]. Specifically, anticholinergic drugs are associated with frailty, falls, hip fractures and reduced independence on ADL[31]. The overuse of proton pump inhibitors in older patients is associated with vitamin B12 deficiency, reduced calcium absorption, hip fractures and overall mortality[31].

For all these reasons, polypharmacy should be reduced and the patient's drug prescriptions should be periodically reviewed in order to prevent or manage frailty[31]. In already frail elders, some drugs may be useful strategies to indirectly manage or treat frailty by controlling chronic diseases (e.g.: diabetes), sarcopenia and neuroendocrine dysfunction (which can lead to anorexia of ageing and undernutrition)[31].

Despite the complexity, the frailty process can be sensitive to treatment and interventions, based on the underlying causes such as social, environmental and financial support, medical conditions and medication (polypharmacy), nutrition and nutritional status (malnutrition and sarcopenia), cognitive status, functional and physical status, mood disorders and sensory abilities[1,12].

Frailty models

There are two main models well accepted in the scientific literature to explain frailty and most of its complexity: the cumulative model and the physical model[3,34]. Both share the idea that frailty is not only a multifactorial state of vulnerability that increases the risk of several adverse outcomes and death, but also an ageing-changeable individual characteristic[1].

The concept of accumulation of deficits, developed by Rockwood et al., proposes that frailty should be assessed through multiple dimensions by a quantitative and objective estimate of the accumulation of deficits which are clinical conditions and diseases[35]. The core ideas are that (1) frailty is a dynamic state, meaning that it can change over the life course, and that (2) frailty underlies the variable vulnerability to negative health outcomes in individuals with the same biological age[1]. The rationale is that with ageing, people are more likely to die, but the risk of death is variable between individuals of the same age. This variability can be related to the fact that older people are more likely to have one or more conditions affecting their general health. The cumulative effect of harmful conditions is different between individuals and can influence their likelihood of death[1,35].

The physical model, known as Physical Frailty Phenotype (PFP), was proposed by Fried et al. and assesses frailty mostly by physical performance, weight loss and exhaustion[3,10]. PFP has proven a high predictive validity and is commonly used in clinical practice[34]. Besides this, the lack on including cognitive, mental health, and social domains makes it insufficient according to some researchers[34].

Diagnosis

Universal consensus regarding the operational criteria in the different practice settings to assess frailty is lacking[1,3,34]. It seems clear that early interventions may be the key to prevent frailty, but also the screening of the potential risk factors becomes crucial[1,3].

Assessment tools

The high prevalence of frailty, its outcomes and its possible preventability became an increasing source of interest in geriatric medicine[4,34]. The early identification of older adults at risk of frailty should be included in the routine assessment of patients, allowing its early identification and thus to plan an cause/problem-centred personalized intervention[9,34].

The primary care is considered the core component of the healthcare system where frailty must be first screened in order to apply preventable strategies and/or treatment interventions[3,34].

An ideal screening tool should be easy to apply in clinical practice and allow a rapid identification of the elders at risk of developing frailty or already frail[12].

Since 1980 the number of publications regarding frailty increased exponentially, as well as the number of tools developed to assess it[12,34,36].

A systematic review identified 26 questionnaires and 8 indicators of frailty, from which the Frailty Index (FI) created from the cumulative model of frailty, and the gait speed showed to be the most useful in routine care in a community perspective[1,3,12,34,37]. In fact, slow walking speed itself has been considered a good indicator of frailty and its outcomes, since a gait speed >1.2m/s is associated with high life expectancy and <1m/s with frailty, disability, and decreased survival[19].

In the FI, deficits on physical, cognitive, mental and functional domains are measured and summed[34,35]. The time consuming and difficulty to implement on daily clinical practice are disadvantages of this tool[34].

Besides this, the PFP is the most used and cited instrument to assess frailty, mainly in community-dwelling settings, followed by the FI, the Gill Frailty Measure, the Frailty Assessment, and the Clinical Frailty Scale (CFS)[1,3,12,38].

According to the PFP, the presence of at least three of the following condition leads to the diagnose of frailty[4,10]:

1. Unintended weight loss of 4.5kg or >5% over one year
2. Slow gait speed according to standardized cut off values for gender and height
3. Self-reported exhaustion from the Center for Epidemiological Studies depression (CES-D) scale (3-4 days per week or most of the time)
4. Low energy expenditure or low physical activity (according to the modified Minnesota leisure time activity questionnaire: <383kcal/week and <270kcal/week for men and woman, respectively)
5. Weak hand grip strength stratified for gender and body mass index (BMI)

When less than three of the described criteria are present, the prefrail diagnostic should be considered[10].

To assess all these diagnostic criteria, the elder must be able to comply, relatively well (both physical and mentally), to perform the required tasks, and so the validation study performed by Fried et al. included a list of exclusion criteria such as Parkinson's disease (PD), stroke, history of depression, and CI[10,17]. For these reasons, the PFP has been tested mostly in older adults with a relatively good health status and in community-dwelling settings[17,34,38,39].

A cross-sectional study from Joanna B. et al., examined the usefulness and diagnostic limitations of the PFP when applied to a geriatric subacute ward. From a sample of 500 elders with a wide range of comorbidities, 35% of the sample were not able to complete the assessment on one or more components mainly due to physical or CI, and thus not diagnosed[17]. This group, compared with the group that performed the all five assessments, were older, had higher prevalence of dementia, lower BMI, and more functional dependent[17]. In conclusion, the application of this instrument in elders with multiple comorbidities, including functional and CI, may be a challenge yet useful despite the diagnostic limitations[4,17]. Further studies on the need to adjust the assessment instruments to the different population characteristics would be useful[17].

The FI compiles impairments in domains such as cognitive status, mood, motivation, mobility, balance, bowel and bladder function, nutrition, social resources, and others,

in a total of 70 items[35,40]. Due to the high extend of this instrument, the CFS was created as a short version, 7-point scale from the original 70 items[40,41]. Based on the FI score, the elders can be classified from fit to frail with a high predictive value of institutionalization and death[35,40].

The CFS is nowadays presented as a 9-item scale that classifies the patient from very fit to terminally ill[42].

The PFP and the CFS are considered two short instruments, and therefore timesaving in clinical practice, and suitable predictors of mortality in older patients admitted at geriatric wards[12]. The CFS also predicts secondary outcomes such as rehospitalization[12].

Most of the validation studies for different instruments to assess frailty excluded dementia or CI (assessed by the Mini Mental State Examination (MMSE)) and/or PD[40].

In 2008, Amici and colleagues designed an 11-item scale, the Marigliano-Cacciafesta Polypathological Scale (MCPS), that assesses the presence and severity of frailty by identifying and classifying the possible severity of disorders related to 11 physiological systems (Neurological disorders, cardiopathy, respiratory, renal, and locomotive apparatus disorders, sensory deprivation, metabolism and nutritional status, cognitive state and mood, peripheral vascular system, oncology, and gastroenteric disorders)[5]. This scale, showed a correlation with the main indices of disability[5]. Amici et al. applied the MCPS to 180 elders with a mean age of 80 years along with assessment of ADL (Katz, and Lawton and Brody scales), Barthel index, Global depression scale, MMSE, Tinetti test for balance and gait, and Mini Nutritional Assessment (MNA)[5]. Strong correlations between MCPS and these scales were demonstrated, making the MCPS a useful tool to assess frailty[5].

Frailty and Neurosciences

Although frailty and neurodegenerative diseases, such as Alzheimer's disease (AD), PD, and amyotrophic lateral sclerosis (ALS), share close concepts including vulnerability, susceptibility, and homeostatic reserves, only recently the field of

neurology has begun to investigate and document these concepts at a neuronal cells level, brain networks, and functions[43].

The concept of frailty can be applied, for example, to try to explain the occurrence of psychotic disturbances or sudden worsening of cognitive abilities, when a patient is subjected to general anesthesia. This can indicate that some brain components, networks, and functions are intrinsically vulnerable and can contribute to the individual's vulnerability to stress events[43].

Also, the concept of reduced physiological reserves that is applied to frailty has been used in neurology to explain, for instance, the differences between individuals when facing similar brain modifications with ageing and pathologies. This has been mainly documented in the cognitive field – cognitive reserve. It has been showed that individuals with a higher education have a reduced risk of developing AD, supposedly due to having higher reserves. Additionally, individuals with higher reserves have more likelihood of maintaining adequate functioning in critical situations such as anesthesia, dehydration, and metabolic syndromes, and tolerate a greater amount of structural and functional disease-specific pathology (like AD or PD)[43].

Although many operational definitions on frailty have been developed, in clinical practice its identification is still not easy or consensual. From the neurology field perspective, two features should be considered: cognitive abilities and emotional status. Both can affect the individual's vulnerability and resiliency, leading to an increased risk of negative outcomes[1].

Even though the concept of frailty refers mainly to the physical components, the CI has been proposed as a potential contributor to the vulnerability of older adults and also a strong and independent predictor of increased risk of mortality, disability, institutionalization, and physical frailty, independently from the clinical diagnosis[44]. The association between CI and frailty could be explained by the interference of declined cognitive abilities in the (1) adherence to health interventions, (2) on maintaining a healthy lifestyle, and (3) recognizing signs and symptoms of diseases. Also, CI can limit planning and the implementation of strategies or adaptive behaviours to respond to stress events[43].

All these reasons justify the inclusion of CI as a key component of frailty[1]. On the other hand, if CI is detected too late, and neurodegeneration has already occurred, there may be no preventive or modifiable intervention that could modify the progression to dementia and/or frailty[43]. This makes its implementation controversial.

Nevertheless, the concept of "cognitive frailty" has emerged as a "*heterogeneous clinical manifestation characterized by the simultaneous presence of both physical frailty and CI*"[1,44]. This condition shares the same rationale of physical frailty (reduction in cognitive/brain reserves), and is characterized by the presence of two core features: presence of both physical frailty and CI, and no diagnostic of other dementia syndromes (such as AD and other dementias)[1,44]. The CI should be diagnosed by a score of 0.5 on the Clinical Dementia Rating Scale (CDR)[45].

Cognitive frailty can negatively influence the health outcomes in physical frail elders[1]. When assessing frailty, the emotional status also requires consideration, since anxiety or depression, and other emotional responses, have well-established interactions with the nervous, endocrine and immune systems, and can trigger the onset and increase the severity of medical conditions. Also, emotional dysregulation can influence the adoption of unhealthy behaviors, increasing the risk of developing consequent diseases and reducing the compliance to interventions[43].

Emotional disturbances are potentially treatable with pharmacological but also non-pharmacological interventions (such as psychotherapy) and, therefore, a potentially modifiable contributor to frailty[43].

The major features of frailty and neurodegenerative diseases, such as PD and dementia syndromes, share common symptoms such as balance and gait impairments, delirium, fluctuating confusion and impaired awareness, and disability that fluctuates over time[1,10,46,47]. For these reasons, it seems reasonable to hypothesize that the prevalence of frailty in this population is high[1,10,46,47].

Evidence of the prevalence of frailty in PD is lacking, possibly because most studies on frailty exclude PD[48]. Frailty and PD share the appearance of physical vulnerability and thus, in clinical practice, the presence of frailty can be misinterpreted as a functional

decline[48]. In a small sample of 49 ambulatory elders with PD, 16 were frail and were at a more advanced stage of the disease[48].

The concept of dementia is defined as a clinical syndrome characterized by a global CI, memory decline and impairment of, at least, one other cognitive domain (executive function or language, for instance)[29]. For a patient to be diagnosed with dementia there must exist a decline from the previous level of cognitive functioning, associated with functional impairment and frequently with mood and behaviour changes[29,49]. AD represents the most common type of dementia syndrome (at least 50% of the cases), although other conditions can cause dementia such as vascular lesions (vascular dementia), Lewy body disorders such as dementia associated with PD and Lewy body dementia (LBD), and frontotemporal dementia (FTD)[49]. Delirium, infections, both urinary and faecal incontinence, and constipation are frequent in dementia syndromes[26]. The clinical course of advanced dementia include complications such as pneumonia and eating problems, that are associated with high 6-month mortality rates[50].

The prevalence of dementia is increasing, causing a high burden on patients, families and societies[26,29,51]. It is estimated that 32% of AD elders (mild to moderate) living in the community are frail, although more advanced stages of the disease and a higher dependency should be factors that increase this prevalence[52].

ALS is a fatal and complex motor neuron disease characterized by the progressive atrophy of skeletal muscles due to the loss of both upper and lower motor neurons[53–55]. Although the mean age of the onset is 60 years old, is recently being hypothesized that some cases of ALS in older adults are underdiagnosed due to atypical clinical presentation, influenced by confusing factors such as comorbidity, weakness, dysphagia, muscle atrophy, and frailty[55]. The prevalence of frailty in ALS patients in unknown.

Frailty and other conditions

Frailty and its association with other diseases have been a source of growing interest due to the possible influence of frailty in poor outcomes[56].

Some of the major preventable chronic respiratory diseases (CRD) such as asthma, chronic obstructive pulmonary disease (COPD), and sleep apnea syndrome are strongly associated with poor outcomes when frailty is present[56]. These conditions are associated with low quality of life, disability, mortality, and unhealthy ageing by contributing to physiological inefficiencies, increased vulnerability to the onset and faster progression of diseases, as well as impaired physical and mental performances[1].

COPD is a major source of physical and social disability, and many patients experience low body weight and undernutrition[1]. Also, older adults with COPD seem to have an increased risk to develop frailty[57].

Diabetes is a prevalent chronic disease in the elderly that can be inter-associated with frailty[1,16]. In older adults, this metabolic condition can have an impact on physical and cognitive function, and quality of life, since usually it coexists with other comorbidities such as heart disease, stroke, and other geriatric syndromes that include CI, urinary incontinence, pain, and depression[1,16]. Diabetic elders also have an increased risk of developing vascular dementia and AD[16].

Diabetes is thought to more than double the risk of developing frailty, due to accelerate the ageing process, to promote sarcopenia, and to contribute to weakness, exhaustion, slowness and low physical activity – core components of frailty[1,16].

Although frequently under-considered, oral health problems are common in older adults. During ageing, conditions such as tooth loss, the use of dental prostheses, the presence of xerostomia, and presbyphagia may occur[1]. The risk of frailty is higher in elders with fewer teeth and that don't compensate with dental prostheses[1]. Additionally, dental problems are strongly associated with poor nutritional outcomes due to chewing and swallowing difficulties leading to weight loss and malnutrition[1].

Frailty, Nutritional status and Nutrition

Nutrition is a key factor and an important health modulator in the older population, since an inadequate nutrition contributes to the complexity of frailty's physiopathology and to the development of sarcopenia[1,24,58,59].

Nutritional status

The rationale behind the importance of nutrition is simple: it is supposed to provide the energy and nutrients needed for the maintenance and correct functioning of all organs and vital systems[1,24]. When nutrition fails to provide the adequate amounts and/or quality of nutrients and energy, whether due to inadequate intake, absorption or metabolization, the nutritional status can deteriorate causing malnutrition[24].

Undernutrition is defined as a state resulting from a lack on the uptake or intake of energy and nutrients, leading to changes on body composition (decreased fat-free mass), decrease of physical and mental function as well as impaired clinical outcomes from disease (immune dysfunction, more frequent hospitalizations and readmissions)[60–62].

Although the acknowledged importance of malnutrition (both under and overnutrition) to the clinical outcomes, due to the complexity of its aetiology and presentations, a gold standard method to assess it is still missing[59,63]. In 2015, the European Society for Parenteral and Enteral Nutrition (ESPEN) published a consensus statement on the diagnostic criteria for undernutrition to unify terminologies in clinical practice[61]. The first step to diagnose undernutrition should be to perform a nutritional screening through validated tools such as Malnutrition Universal Screening Tool (MUST) or MNA[61]. In those screened as at risk, the undernutrition should be considered in those who have one of two conditions:

1. BMI <18.5kg/m^2 **or**
2. Unintentional weight loss >10% in an indefinite time or >5% over the last 3 months **plus** BMI <20kg/m^2 (<70 years old) or <22kg/m^2 (≥70 years old) **or** fat-free mass index (FFMI) <15kg/m^2 in women and <17kg/m^2 in men[61].

Despite this, in almost every study published regarding the prevalence of malnutrition, the variation of methods to assess it implies a variation of results[63,64]. This greatly limit the data analysis and comparison[25].

Older adults are more vulnerable to malnutrition as they present multiple risk factors[58,60,63]. A systematic review, based on longitudinal data, show that the ageing process *per se*, polypharmacy, frailty, constipation, cognitive decline, dementia, eating

dependence, poor appetite, dysphagia, and institutionalization, are risk factors highlighted as significant contributors to malnutrition[60]. The diagnose of PD was also a stated risk factor[60].

The decline in functional and cognitive abilities can lead to institutionalization, which also increases the risk of malnutrition[59,63,65,66].

Acute and chronic diseases in this population increase even more the risk of malnutrition, since the nutritional problems exacerbate, and the nutritional intake is often affected[58].

The clinical consequences of malnutrition regarding its relation to poor outcomes are well-documented: increased rates of pressure ulcers and infections, increased periods of hospitalization, higher mortality, and increased time for convalescence after acute illness[58]. Also, undernutrition is associated with other geriatric syndromes such as sarcopenia, insomnia, psychosis, dementia, depression, delirium, and neurological disorders[58,66]. These factors increase the risk of falls and functional dependence[66].

The prevalence of malnutrition in the elderly is heterogeneous and rises as the level of care increases[58,62,67,68]. In community setting, is estimated that malnutrition affects 5 to 30% of elders, while in residential care facilities it rises to 16 to 70%[63].

Nutritional status and frailty share a close relationship, being estimated that 90% of community-dwelling elders at risk of malnutrition are either prefrail or frail[69]. Malnutrition seems independently associated with frailty[70].

It is generally accepted that neurodegenerative disorders, such as dementia, PD and ALS, increase the risk of malnutrition[71,72].

In institutionalized elderly, with neurodegenerative disorders, the prevalence of undernutrition, at the moment of institutionalization, is 77% according to the MNA and 46% according to BMI[72].

PD is the second most common neurodegenerative disorder worldwide, being estimated that in Portugal 180 of 100.000 inhabitants aged over 50 years old have the disease[64,73]. Lower BMI and unintentional weight loss have been reported as more prevalent in PD than aged-match controls. The duration, stage and severity of the disease are associated with significant decrease in BMI and body weight[64]. PD patients present a higher risk

of developing sarcopenia. In older adults with idiopathic PD, sarcopenia is common (18-41%, depending on the operational criteria) and also associated with disease severity[74,75].

Motor symptoms of PD include bradykinesia, rigidity, akinesia, and resting tremor which can influence the patients' ability to shop and cook independently, that lead to increased risk of malnutrition[64]. Also, non-motor symptoms such as constipation, dysphagia, olfactory dysfunction, hyposmia, delayed gastric emptying, early satiety, sialorrhea, depression, dementia, and apathy, play a significant role on the nutritional intake and can contribute to malnutrition[64].

Malnutrition in PD is estimated to affect 0 to 24% of community-dwelling patients, while 3 to 60% are considered at risk[64].

Patients with dementia frequently present nutritional problems or disrupting eating behaviours that lead to increased risk of malnutrition[29]. Weight loss is considered an important feature of dementia that can begin before the diagnose and becomes more frequent with the course of the disease[29]. The reported prevalence of malnutrition in older adults with dementia is 47.8%[76]. LBD and vascular dementia present a higher prevalence of malnutrition in community-dwelling patients (77% and 49% at risk, respectively)[76].

In early stages these patients can have problems on planning, shopping, preparing and cooking food and meals, and progress to forget to eat or that already ate, apraxia for food and/or utensils, eating dependence, behavioural problems such as agitation and hyperactivity during meals[29]. Also, 13 to 57% of the patients develop dysphagia that is more common in late stages of FTD and AD[29].

ALS patients present multiple risk factors for malnutrition: dysphagia, anorexia, depression, weakness of abdominal and pelvic muscles that prolongs meals time and fatigue, constipation, muscle atrophy, and increased energy expenditure by the respiratory system[53]. Malnutrition is considered an independent prognostic factor during the follow-up of ALS patients, while weight loss is a prognostic factor both at the diagnosis and follow-up[53].

In many ways, frailty and nutritional status share similar concepts, as the same difficulty on standardizing a definition and gold standard methods to assess, widely variation on the reported prevalence, and multifactorial aetiology[1,61].

Nutritional status assessment should be a comprehensive and multifactorial approach, much as a frailty assessment should be[24,29,53,61,77].

Body weight and Body mass index

Weight loss, low BMI, and undernutrition demonstrate to be important indicators of frailty[1,78]. In fact, weight loss is included in several tools to assess frailty such as the PFP[78].

Although much attention is being paid to low BMI and undernutrition, recent studies have found a possible association between high BMI and obesity with frailty[1,78,79]. This is particularly important since overweight and obesity prevalence in elderly has been increasing over the years and a gradual reduction of skeletal and bone mass can occur unnoticed due to high body volume[1,78,80–82]. Blaum and colleagues were the first authors to demonstrate that prefrail and frail women aged over 70 years had a significantly higher prevalence of overweight and obesity[1,83].

In Esquinas et al. study, the odds ratio for obesity and abdominal obesity and the risk of frailty was 1.73 and 1.67, respectively[84]. The authors also showed that obesity was associated with increased risk of exhaustion, low physical activity, and weakness – important components of physical frailty[84].

Studies have shown that the association between BMI and frailty can be translated in a U-shaped curve, meaning that both low and high BMI are related to the development of frailty[1,78]. Rietman and colleagues have compared the BMI values in frail elderly in different domains such as physical frailty, cognitive frailty, social frailty and psychological frailty, and found higher prevalence of physical frailty in BMI under 20 kg/m^2 and over 30 kg/m^2. In psychological and social frailty domains, no association with BMI was found[78]. These results were concordant with Hubbard et al. conclusions, particularly in relation to BMI, but that there is also a high prevalence of frailty in

patients with high waist circumference (≥88 cm for women and ≥102 cm for men)[78,79,84].

In obese older adults, the intentional or non-intentional weight loss might have unwanted functional effects such as loss of lean and bone mass, which can lead to sarcopenia and frailty[1,58,85–87]. Therefore, it's extremely important that both nutritional and physical interventions have in consideration the goal of, at minimum, to prevent the loss of lean mass (preferably to increase)[1]. The benefits and potential risks of promoting these interventions in frail elders to change simultaneous body weight, body composition and functional abilities, should be considered[1,85–87].

Although a BMI up to 30kg/m^2 is correspondent to being overweight, it has been showed to be a protective factor against morbidity and mortality in older adults, so an intervention should only be planned aiming weight loss in elderly with BMI > 30kg/m^2 [88]. In these individuals, maintaining or improving muscle mass should be a major goal of the intervention, with greater reach of effectiveness when exercise and nutrition interventions are combined[1,87]. A moderate energy restriction (200-500kcal/day), a protein intake of at least 1g/kg body weight/day, and an adequate intake of micronutrients, associated with exercise or physical activity to promote a moderate weight loss (0.5-1kg/week or 8-10% of initial body weight in a 6 months period) is recommended[1,85,88].

BMI, as a single diagnostic criteria for nutritional status is not sensitive to body weight changes such as weight loss, so it should be used in combination with other nutritional parameters[64].

Weight loss and underweight, as a result of inadequate intake of energy and protein, are important contributors to poor nutritional status and decreased reserve capacity[6,10,64]. This weight loss is associated with decrease of skeletal muscle mass, that leads to lower muscle strength, exhaustion, reduced physical performance and activity – all considered manifestations of physical frailty[6].

Nutritional assessment tools

Nutritional status assessment through validated tools is recommended as they include multiple domains related to nutritional problems and allow a unify multifactorial assessment[64,77].

Regarding neurodegenerative disorders, no specific nutritional assessment tool is recommended.

MNA is validated for older adults independently of the setting (community, nursing home or hospital) and is one of the most widely used tools, including for neurodegenerative patients[29,58,64,89]. Nutritional status assessed by the MNA was demonstrated to be associated with frailty[69,90,91].

Nutrition – a risk factor and a therapeutic intervention

In the elderly, the main goal of nutrition should be to provide adequate amounts of energy, macro and micronutrients, and fluids in order to improve or to maintain an adequate nutritional status and to contribute to improve functional capacity and quality of life[58].

Nutrition have been evidenced to be an important factor associated with the development of both sarcopenia and frailty, as well as a major contributor or influencer on many of the components involved on frailty onset and progression[1,92]. Also, the characteristics of frailty have many features that can be related to nutrition, specifically to insufficient nutrition: muscle weakness, sarcopenia, and fatigue[1,6].

The contribution of diet to the mechanisms that lead to frailty remains unclear. Nevertheless, diet quality, healthy food choices and food diversity are correlated with frailty[1,36,93].

Instead of focusing only in specific or single nutrients, the whole dietary pattern should be analysed and modified and/or improved regarding preventing or treating frailty[1]. A diet rich in nutrient-dense foods and low on saturated fats seems associated with lower risk of frailty[1,6,94,95]. Such characteristics can be found in the Mediterranean diet (MD). MD is characterized by a combination of different types of food and nutrients with potential protective effects against chronic and inflammatory conditions[30]. High intake

of sources of polyunsaturated fats (nuts and fish) and fiber (vegetables, fruits and whole grains), combined with a moderate intake of dairy products, olive oil (as a source of monounsaturated fats) and moderate alcohol consumption are the main features of this dietary pattern[30,95–98].

Higher adherence to MD has been inversely associated with functional impairment and frailty, as well as a protective dietary pattern against chronic diseases such as diabetes and AD[30,36,95–99].

A recent prospective study performed with 560 non-frail French older adults showed that the incidence of physical frailty was associated with low adherence to the MD[96]. Also, MD adherence was associated with a significant reduction of the risk of slowness, poor muscle strength and low physical activity[96].

Energy

The imbalance between energy intake and expenditure compromises the metabolic functioning of physiological systems[36]. Catabolic response of muscle and fat tissues occurs when the energy intake is insufficient to meet energy needs, compromising functional abilities and the occurrence of weight loss[36]. Thus, the maintenance of muscle mass highly depends on the energy intake[36].

Older adults often present anorexia of ageing, defined as the loss of appetite associated with ageing, that is partially explained by changes in taste and/or smell, slower gastric emptying and endocrine dysfunction, chewing and/or swallowing problems, CI, and comorbidity that may negatively affect energy and nutrient intake[36,100–102].

The anorexia of ageing is more prevalent in frail elders and is considered a modifiable risk factor for frailty[36,100–102].

In 34% of institutionalized older adults the energy intake is lower than the recommended[6]. Frail older adults seem to have insufficient intakes of energy, protein and/or other nutrients when compared to non-frail elders[1,36].

A daily energy intake ≤21 kcal/kg body weight/day was found significantly associated with frailty in a sample of 802 elders[103]. In the same sample, the low intake of protein, vitamin D, E, C and folate were also associated with higher risk of frailty[103]. The

authors concluded that a low intake of more than three nutrients were independently related to the presence of frailty[103].

Protein

The imbalance between protein needs and real intake promotes loss of skeletal muscle mass, loss of strength, sarcopenia and physical disability that, in other words, promotes frailty[36,104]. Along with low protein intake, muscle disuse due to bed rest or low physical activity leads to a change in the protein synthesis and breakdown and muscle atrophy[36,104].

Evidence shows that 35% of institutionalized elderly fail to ensure the minimum protein intake to maintain muscle integrity (0.7g/kg/day) due to physiological changes, comorbidity, physical and mental disabilities and age- and/or disease-associated anorexia[36,104].

Lower incidence of frailty has been observed in older adults with higher protein intake, meaning that a possible goal for nutritional interventions on frailty should be to promote an adequate intake of protein[1,105,106]. A French cohort study found significant associations between lower prevalence of frailty and a protein intake of 1g/kg body weight/day or higher[107].

Besides predicting frailty, low protein intake also predicts low bone mass and osteoporosis, that increases two times the risk of developing frailty[104].

The specific role of the source of protein ingestion (animal vs vegetable), specific amino acids (AA) or even the timing to consume protein can be relevant factors regarding the anabolic effect of protein intake, however few studies have been performed so far[1]. In 2016, a prospective study concluded that the total daily intake of protein was inversely associated with the incidence of frailty[105].

To date, only one cross-sectional study found a possible relation between the distribution of protein intake during the day and frailty[108]. In a sample of 194 community-dwelling elders, the authors found that frail participants had a significant lower intake of protein in the morning than the pre-frail and non-frail[108]. In the same study, the total amount of protein intake was found not to be related to frailty[108].

Micronutrients

Micronutrient deficiency is common in the elderly[109]. In Semba *et al* study, the number of micronutrient deficiencies was associated with increased risk of frailty in older women, in which each deficiency increased the risk in 10%[109]. Low intakes of vitamins A, C, D, E, B6 and folate have been pointed as related to frailty[106].

The evidence of supplementation of micronutrients is also scarce and heterogeneous, as well as little studied besides healthy and non-frail elders or in sarcopenia[1].

In conclusion, although is generally accepted that the modification of nutrition quality could improve strength, walking speed, and nutritional status of frail elderly, the available evidence is limited to ensure this hypothesis and to develop an intervention[1]. Since there is no available guidelines for nutritional intervention specifically in frailty, the principles of the nutritional care process for older adults should be applied, namely screening, assessment, defining goals, planning and implementing an intervention, monitoring, updating goals and intervention, and periodic reassessment[58]. Nutritional therapy in order to improve nutritional status and functional abilities should be implemented as a component to the treatment of frailty[6,67,105,110].

Nutritional therapy

Currently, no specific dietary recommendations were published to treat frailty. The nutritional therapy in frail older adults should follow similar orientations than those for geriatrics, adjusted and individualized regarding nutritional status, physical activity, disease and tolerance[58].

The nutritional intervention should aim to provide an energy intake of 30kcal/kg of body weight/day[58]. In ill older adults, a minimal of 27 to 30kcal/kg/day is recommended, while for underweight elders it should rise to 32 to 38kcal/kg/day[58].

Protein intake recommendations for both adults and older adults are 0.8-1.0g/kg of body weight/day[104]. However, in 2014, ESPEN highlighted the importance to increase protein intake in elders for preservation of lean mass, functionality and general health[104].

The current reccomendations for healthy older adults are 1-1.2g/kg/day, while for older adults with acute or chronic diseases the goal should be 1.2-1.5g/kg/day[104]. Institutionalized older adults often present multiple chronic conditions, and thus greater protein needs[104]. In severe illness, injury or malnutrition the daily amount of protein can rise up to 2g/kg/day[58]. Specifically for frailty, the scientific evidence is scarce regarding protein intake[58].

Besides the potential, reliable evidence on randomized-controlled trials (RCTs) regarding the role of protein intake is scarce, and most of the studies have been focusing on sarcopenia or their samples only included healthy elders[1].

The oral nutritional supplements (ONS), namely those rich in energy, protein, and micronutrients, seem a promising treatment option for frailty[1]. These products should be provided as treatment options in older adults with malnutrition or at risk of malnutrition with chronic conditions, institutionalized or community-dwelled, when dietary counselling and food fortification and enrichment are insufficient to reach nutritional intervention goals regarding nutritional intake, body weight, and reducing the risk of functional decline[58].

The ONS should provide at least 400kcal/day and at least 30g/day of protein in case of malnutrition or risk of malnutrition[58]. The efficacy and benefits of starting ONS should be assessed once a month[58].

A systematic review of Cochrane stated that supplementation of energy and protein produces small but consistent weight gain in older adults, as well as reduces mortality[111]. However, no evidence was found that ONS improved functional abilities or reduced the length of hospitalization[111].

Although the growing evidence of the benefits of ONS in undernourished older adults in multiple settings, the currently available evidence regarding these products and the treatment of frailty is scarce[1,58,112–116].

Specifically, in institutionalized frail older adults, the research and evidence are little[117]. A small RCT with 50 frail nursing home residents showed high compliance with the intake of a ONS during a 10 weeks intervention[117]. However, no significant increase on

the total energy intake was observed and the overall nutritional status or functional status didn't significantly improve[117].

Therapeutic interventions

Frailty is a multifactorial syndrome, which implicates a multidisciplinary approach based on individualized and comprehensive assessment of older adults[1,118].

Guidelines to provide a line of treatment or prevention for frailty are currently lacking[118,119]. The main response from the health care systems to frailty is reactive to the acute situations such as falls, delirium and immobility[119].

Inadequate nutrition, poor nutritional status, depression, physical inactivity and polypharmacy are potentially treatable causes for frailty[1,9].

The combination of adequate nutrition (with or without supplementation) and exercise are recommended to improve lean mass, physical performance and to treat/attenuate frailty[1,120]. The combination of nutritional (nutritional supplementation), physical (physical training), and cognitive (cognitive training) interventions in frail older adults seemed effective in reversing frailty in a sample of community-living elders[121]. In this study, beneficial effects of the interventions were observed after 3 months[121].

Exercise programs improve functional abilities, reduce the risk of falling and increase the quality of life of frail older adults[122]. In older groups, promoting long-term adherence is important to promote a regular and feasible training regarding intensity and type of exercises[122]. Resistance-training should be performed weekly (2-3 times) at the beginning and then added power-training to more efficiently improve and maintain muscle quality[122]. Functional abilities should be improved by combining the training with ADL stimulation[122]. Aerobic exercise is also recommended, including walking, treadmill, stair climbing and cycling. The exercise programs should always be individualized to the elders considering safety, functional and cognitive abilities[122].

Research objectives

The primary objective of this research project is to describe the frequency of frailty in institutionalized patients with neurodegenerative disorders in the moment of admission in a healthcare institution.

The secondary objectives are:

a) To describe the frequency of undernutrition and risk of undernutrition in the moment of admission
b) To evaluate the correlation between frailty and nutritional status in the moment of admission
c) To compare the frequency of frailty and undernutrition one and three months after admission
d) To evaluate the correlation between the MCPS and CFS.

Methods

Study design

A cross-sectional observational pilot study was performed to meet the proposed objectives of this study. A component of prospective study design was added to meet secondary objectives regarding reassessments of one and three months after admission.

Scientific and Ethics approvals

The research project was approved by both the Scientific Board of the Faculty of Medicine of the University of Lisbon (FMUL) and by the Ethics Committee of Campus Neurológico Sénior (CNS) in 21st November 2017 and 1st February 2018, respectively.

Study duration and data collection

Data collection was performed for 4 months.

The research units involved were:

a) CNS, Torres Vedras, Lisbon, Portugal – where participants were recruited, and data was collected;
b) FMUL and Lisbon School of Health Technology, Instituto Politécnico de Lisboa (LSHT).

Inclusion and exclusion criteria

All patients with 65 years and older, with at least one of the following neurodegenerative disorders, consecutively admitted in CNS, were screened for inclusion and exclusion criteria:

a) Dementia Syndromes, such as AD, FTD, Vascular dementia (VD) and other non-specified dementia syndromes;
b) Parkinsonian Syndromes, such as PD, LBD, Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Multiple System Atrophy (MSA) and Vascular Parkinsonism (VP);
c) Motor Neuron Disease.

A written informed consent to participate in the study was provided to all patients who meet the inclusion criteria. This consent was obtained from a legal representative if the patient had dementia.

Patients with major lower limbs oedema were excluded due to the risk of overestimating anthropometric measurements such as calf circumference.

Outcomes

The primary outcome is the frequency of frailty according to the MCPS, namely slight, medium, medium-severe, severe and very severe frailty in institutionalized patients with neurodegenerative disorders in the moment of admission. For purposes of statistical analysis the global frequency of frailty is considered the sum of the frequencies of medium-severe, severe and very severe frailty from the MCPS.

The secondary outcomes are:

a) The frequency of undernutrition according to the Mini Nutritional Assessment in the moment of admission.
b) The correlation between frailty and the different criteria for nutritional status in the moment of admission.
c) The frequency of frailty and undernutrition one and three months after the admission.
d) The correlation between the MCPS and CFS.

Materials

Information sheet

An information sheet was prepared to participants, explaining the research project title, the purpose of the study, procedures, possible benefits, predictable physical risks, voluntary participation and right to drop out, the use of data and investigators contacts (annex I).

Informed consent

All participants and/or legal representatives signed an informed consent form. As a research unit, CNS has its own institutional informed consent form that is presented in the moment of admission by the nurse who receives the patient and/or caregiver (annex II).

Case report form

A case report form (CRF) was developed to collect all the patient-relevant data regarding procedures specified by the assessment protocol (annex III).

Statistical analysis

The distribution of the data was analysed by skewness and kurtosis, and normal distribution was considered when the variable followed a symmetric and mesocuric presentation.

All data was analysed using descriptive statistics: categorical variables through relative frequencies, and continuous variables through mean and standard deviation.

The Spearman's correlation test was used to assess the following correlations:

a) The correlation between the MCPS and the CFS
b) The correlation between the CFS and the BMI, mid-arm circumference (MAC), calf circumference (CC), MNA, the Edinburgh Feeding Evaluation in Dementia Questionnaire (EdFED-Q) and the Subjective Global Assessment (SGA)
c) The correlation between the MCPS and the SGA

The Pearson's correlation test was used to assess the following correlations:

a) The correlation between the MCPS and the Hoehn and Yahr scale (H&Y) (severity of parkinsonian syndromes)
b) The correlation between the MCPS and the CDR (severity of dementia syndromes)
c) The correlation between the MCPS and the BMI, MAC, CC, MNA and the EdFED-Q

d) The correlation between the H&Y and the MNA, the EdFED-Q and the SGA

To assess differences between the mean values of independent groups, the Mann-Whitney test was used for the following variables: age, MCPS score, MNA score, BMI value, MAC value, CC value and the EdFED-Q. The difference between median values of categorical variables such as the H&Y, the CFS and the SGA were assessed with the Chi square test.

To compare differences between reassessment moments (admission, one and three-months), the Wilcoxon test for paired samples was used for MCPS and MNA results.

Statistical significance was considered ≤ 0.05 for all tests.

Assessment protocol

Assessment moments and timings

The established moments to perform the assessment protocol were:

a) In the admission: the assessment protocol was performed by the investigator within the first 24-48 hours after the patient was admitted;

b) One-month reassessment: the first reassessment was performed one month after the date of the admission;

c) Three-month reassessment: the second reassessment was performed three months after the date of the admission.

Each assessment moment was composed by a frailty and a nutritional assessment.

Sociodemographic and clinical data

Sociodemographic information was collected in the admission.

The main neurodegenerative disorder diagnosed, and other relevant clinical background were collected from the clinical process. Also, the severity of the disease was rated according to:

a) The H&Y for parkinsonian syndromes[123]

b) The CDR for dementia syndromes[45]

Frailty assessment

There are no specific tools to assess frailty in patients with neurodegenerative disorders. As described in the introduction section (sub-section Diagnosis – Assessment tools), most of the instruments developed to assess frailty excluded some of the neurodegenerative disorders included in the present study, or their results could be different when applied to the studied population (e.g.: PFP), or its application was too extensive for clinical practice (e.g.: FI).

The investigators intended to assess frailty with the same instruments, independently of the diagnose, and tools were selected following the criteria:

1. The structure and content of the scale had to be comprehensive, meaning that most of frailty domains should be included (cognitive, mood, physical, nutrition, and others) and covered a multidisciplinary assessment
2. Not too long and time-consuming to apply
3. Not dependent on the patients' collaboration (either physical and/or mental) or diagnose

Also, we aimed to apply one of the most used scales to assess frailty.

The Marigliano-Cacciafesta Polypathological Scale

The MCPS was developed as a new multidimensional tool to assess frailty[5].

The structure and content of MCPS allows its application to all the participants, independently of the collaboration or diagnose, while not too extensive to apply on clinical practice. Besides its objectivity, the MCPS shares the concept of the FI.

The obtained classification of frailty is: Slight (<15 scores), Medium (15-24 scores), Medium-Severe (25-49 scores), Severe (50-74 scores) and Very severe polypathology (≥75 scores)[5].

Clinical Frailty Scale

The CFS is a short instrument of 9-items (figure 1), derived from the FI, which classifies frailty according to the following:

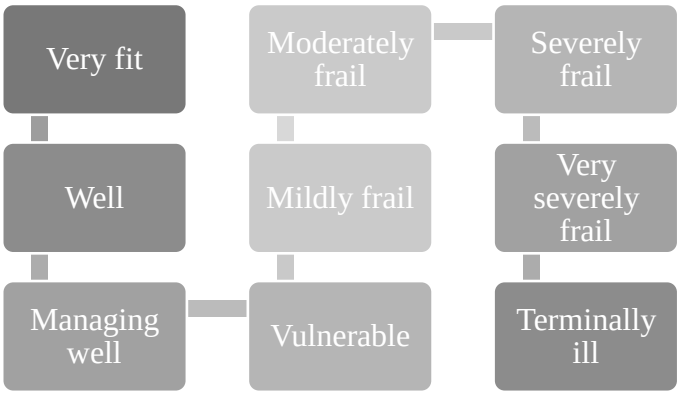

Figure 1. Classification of frailty according to the items of the clinical frailty scale (adapted from Rockwood et al[124]).

This scale bases its assessment mainly on physical performance, appearance, and dependence[124]. The score is obtained by the health professional perception on the patients' global health/frailty according to the detailed descriptions[124].

Nutritional assessment

There are no specific tools to assess nutritional status in patients with neurodegenerative disorders. Nutritional status was assessed according to two validated questionnaires and three non-invasive anthropometric measurements.

Mini Nutritional Assessment

The MNA is a simple and easy to apply questionnaire that assesses nutritional status, and more specifically detects undernutrition[125,126]. This tool is widely used in geriatric populations due to its comprehensive assessment, from community-dwelling to institutionalized elders[125–128].

MNA is composed of two essential parts:

a) The screening tool (MNA short-form), that detects the risk of undernutrition with six questions regarding recent changes in food intake, recent involuntary weight loss, mobility, recent psychological stress or acute disease events, neuropsychological problems and low BMI[127];
b) The assessment tool (MNA full form), that assesses more deeply twelve others factors that can influence nutritional status such as pressure sores, polymedication, nutrient intake, eating dependence, and low MAC and CC[127].

The sum of both parts gives information about the general nutritional status:

a) Normal nutritional status: 24 to 30 points;
b) At risk of undernutrition: 17 to 23.5 points;
c) Undernutrition: <17 points[125,127].

To monitor nutritional status, it is recommended to reapply MNA every three months[129].

Subjective Global Assessment

The second questionnaire used to assess nutritional status in this research project was the SGA[130]. Although it is not one of the most used tools in the geriatric population, SGA performance was considered favourable as a method of nutritional assessment[128,131].

The accuracy of this questionnaire has been questioned due to its subjectivity since the results depend on the experience of the observer on detecting nutritional changes[131]. Besides this, SGA adds important information to patient's nutritional status that can guide and/or help to focus the nutritional intervention, namely gastrointestinal symptoms and severity of recent weight loss[132]. Another interesting feature of this tool is physical examination regarding muscle and fat reserves deficits and fluid status, which allows a monitoring of the general body composition through regular reassessments.

SGA rates nutritional status according to three categories:

- Category A – Well nourished
- Category B – Moderately (or suspected of being) malnourished
- Category C – Severely malnourished

To monitor and to detect changes in nutritional status is recommended to reapply SGA monthly[133].

Body mass index

The body weight of all participants was obtained using a calibrated digital chair scale SECA[134]. The height was obtained from official personal identification cards since most of the participants couldn't keep a straight orthostatic position to allow an accurate measurement.

BMI was calculated according to the equation $\frac{Weight\ (kg)}{Height\ (m)^2}$.

The classification of nutritional status according to BMI was the following:

a) Undernutrition: <22kg/m^2;
b) At risk of undernutrition: 22 to 23.9kg/m^2;
c) Normal nutrition status: 24 to 26.9kg/m^2;

d) Overweight: 27 to 30kg/m^2 for males and 27 to 32kg/m^2 for females;

e) Obesity: >30kg/m^2 for males and >32kg/m^2 for females[135].

Mid-arm circumference

MAC was measured with a measuring tape on the non-dominant arm in the midpoint between the acromion and olecranon[136].

Mid-upper arm circumference percentiles from the Center for Disease Control and Prevention (CDC) were used to obtain a classification of nutritional status according to gender and age[137]. The interpretation was the following:

a) Undernutrition: percentile <15th;

b) Normal nutritional status: percentile 15 to 75th;

c) Overweight/Obesity: percentile >75th [138].

Calf circumference

The measurement of CC was performed in the left leg positioned with the knee at a 90º angle[136]. The thickest part of the leg was measured with a measuring tape[136].

Since in elderly a CC <31cm is a good indicator of muscular depletion and risk of undernutrition, the cut-off of 31cm was used to classify nutritional status:

a) Undernutrition: <31cm;

b) Normal nutritional status: ≥31cm[99].

Edinburgh Feeding Evaluation in Dementia Questionnaire

Eating problems and disruptive eating behaviours are common in patients with dementia, especially in moderate to severe stages[29]. Food or drink refusal, physical disabilities, agnosia, difficulties on chewing and/or swallowing may lead to increased risk of malnutrition and its negative health outcomes[29,139].

The EdFED-Q is a scale developed to quantify the frequency of eating behaviours and eating problems in patients with dementia through 11 questions[140–144]. To each question the health professional must quantify the frequency of that specific behaviour in "0=never", "1=sometimes" and "2=frequently"[139].

Although there are no cut-off values regarding this tool, it may allow to predict the need for assistance and to prevent low food intake and malnutrition[29].

The EdFED-Q is recommended by ESPEN as a validated tool to recognize problems with eating and drinking, helping to plan multidimensional interventions[29].

Results

Population's characteristics

A total of 76 participants (69.7% males) were included on this study in the moment of admission, from which 82.9% were parkinsonian syndromes (table 2). No participant with motor neuron disease was included.

Neurodegenerative diagnose	**Frequency** (%)
Parkinsonian syndromes	**82.9 (n=63)**
Parkinson's disease	39.5 (n=30)
Lewy body dementia	15.8 (n=12)
Progressive supranuclear palsy	6.5 (n=5)
Multiple system atrophy	5.3 (n=4)
Corticobasal degeneration	3.9 (n=3)
Vascular parkinsonism	2.6 (n=2)
Non-specified parkinsonian syndrome	9.2 (n=7)
Dementia syndromes	**17.1 (13)**
Alzheimer's disease	6.6 (n=5)
Frontotemporal dementia	5.3 (n=4)
Non-specified dementia syndrome	5.3 (n=4)

Table 2. Participants' neurodegenerative diagnoses in the moment of admission.

Due to the low number of participants with PSP, LBD, MSA, CBD, VP, and non-specified parkinsonian syndrome, all these diseases were grouped in a single group: "Atypical parkinsonism"[145].

Table 3 displays the sociodemographic and clinical data of the participants.

	All participants (n=76)	Parkinsonian syndromes (n=63)									Dementia syndromes (n=13)			p [b]
		Parkinson's disease (n=30)	Atypical parkinsonism (n=33)	p [a]	Atypical parkinsonism diagnoses									
					LBD (n=12)	PSP (n=5)	MSA (n=4)	Corticobasal degeneration (n=3)	Vascular parkinsonism (n=2)	Non-specified parkinsonian syndrome (n=7)	Alzheimer's disease (n=5)	FTD (n=4)	Non-specified dementia syndrome (n=4)	
Age (years)	76±6.8	75.1±5.5	75.8±7.4	0.68[1]	78.4±8.4	76.6±7.8	72±6.6	74.7±4.0	72.0±1.4	74.6±7.7	80.0±6.6	82.5±10.7	73.0±2.9	0.18[1]
Gender (female/male)	23/53	7/23		-	2/10	1/4	0/4	1/2	1/1	4/3	4/1	2/2	1/3	-
Severity of the disease														
Hoehn & Yahr	4 (4)	3 (4)	5 (4)	0.05[2] *	4 (4)	5 (2)	4.5 (2)	5 (0)	4.5 (1)	5 (3)	-	-	-	-
Clinical dementia rating	2 (2.5)	-	-	-	-	-	-	-	-	-	2 (1)	2.5 (1)	2 (2.5)	-
Frailty														
MCPS	38.3±21.0	31.8±18.1	45.2±22.5	0.01[1] *	43.6±19.9	37.6±17.5	49.5±21.1	76.0±26.9	42.0±29.7	38.1±23.4	26.2±14.8	48.3±24.2	35.0±17.5	0.76[1]
Clinical Frailty Scale	3 (5)	3 (5)	2 (5)	0.31[2]	2 (4)	2 (2)	2 (1)	2 (1)	3 (0)	2 (4)	3 (3)	2.5 (1)	2.5 (2)	0.89[2]
Nutritional status														
MNA	20.3±5.0	21.3±4.7	19.8±5	0.18[1]	19.7±4.1	21.4±3.9	17.8±6.6	14.3±6.3	25.0±0.7	20.9±5.3	18.6±6.5	19.9±6.9	19.5±3.2	0.46[1]
SGA	2 (2)	2 (2)	2 (2)	0.66[2]	1.5 (1)	2 (1)	1 (1)	1 (2)	2 (0)	2 (2)	1 (2)	1.5 (1)	1.5 (1)	0.40[2]
Body mass index	26.1±5.3	26.3±5.1	26.3±5.8	0.69[1]	26.9±7.3	26.2±2.6	25.9±4.9	21.2±5.0	31.3±10.3	26.4±4.2	22.1±2.2	28.5±6.8	25.3±2.9	0.51[1]
Mid-arm circumference	29.1±4.6	29.4±4.4	29.4±4.9	0.79[1]	28.4±5.5	31.5±3.1	27.0±3.9	25.8±2.4	28.3±6.1	32.7±4.6	24.9±3.0	31.6±4.8	27.1±3.0	0.26[1]
Calf circumference	35.4±4.7	35.8±4.5	35.2±4.9	0.67[1]	35.0±5.6	37.2±1.5	35.0±4.1	29.1±7.9	34.9±0.9	36.8±4.1	32.4±3.1	39.5±4.7	33.4±2.6	0.52[1]
EdFED-Q	3.7±3.7	2.6±3.4	4.5±4	0.01[1] *	4.1±3.1	2.8±3.1	4.8±4.1	8.7±6.4	1.5±0.7	5.4±5.0	4.2±1.9	6.0±4.2	2.5±1.9	0.22[1]

Table 3. Sociodemographic and clinical data of the participants in the admission moment.

Mean values ± standard deviation; Median values (interquartile range); MCPS (Marigliano-Cacciafesta Polypathological Scale); MNA (Mini Nutritional Assessment); SGA (Subjective Global Assessment); EdFED-Q (Edinburgh Feeding Evaluation in Dementia Questionnaire); LBD (Lewy Body Dementia); PSP (Progressive Supranuclear Palsy); MSA (Multiple Systems Atrophy); FTD (Frontotemporal dementia); [a] *p* value for the comparison between Parkinson's disease and atypical parkinsonism groups; [b] *p* value for the comparison between parkinsonian and dementia syndromes groups ; [1] *p* value for the Mann-Whitney test for independent samples; [2] *p* value for the Chi square test for independent samples; * Significant

In the first reassessment moment (one-month after the admission), from the 76 initial participants, only 22.4% (n=17) participants were included and 82.4% (n=14) of them had a parkinsonian syndrome. In the reassessment after 3 months only 7.9% (n=6) participants were included, from which 83.3% (n=5) had a parkinsonian syndrome.

The number of participants included in the reassessment moments diminished since the admission moment due to discharge or death.

Frailty

According to the MCPS and the CFS most of the participants were medium-severely frail (46.1%) and severely frail (44.7%), respectively (table 4).

Marigliano-Cacciafesta Polypathological Scale (n=76)		**Clinical Frailty Scale (n=76)**	
Classification	**Frequency** (%)	**Classification**	**Frequency** (%)
Slight	6.6 (n=5)	Managing well	3.9 (n=3)
Medium	22.4 (n=17)	Vulnerable	9.2 (n=7)
Medium-severe	46.1 (n=35)	Mildly frail	10.5 (n=8)
Severe	15.8 (n=12)	Moderately frail	27.6 (n=21)
Very severe	9.2 (n=7)	Severely frail	44.7 (n=34)
		Very severely frail	3.9 (n=3)

Table 4. Frailty frequency according to the Marigliano-Cacciafesta Polypathological Scale and to the Clinical Frailty Scale in the moment of admission.

The MCPS score and the CFS classification were statistically significant correlated (rs= -0.665; p=0.000). This correlation was stronger in dementia syndromes (rs= -0.773; p=0.002), followed by atypical parkinsonism (rs= -0.635; p=0.000) and PD (rs= -0.501; p=0.005).

The frequency of the severity of frailty in the different types of neurodegenerative disorder are presented in figure 2.

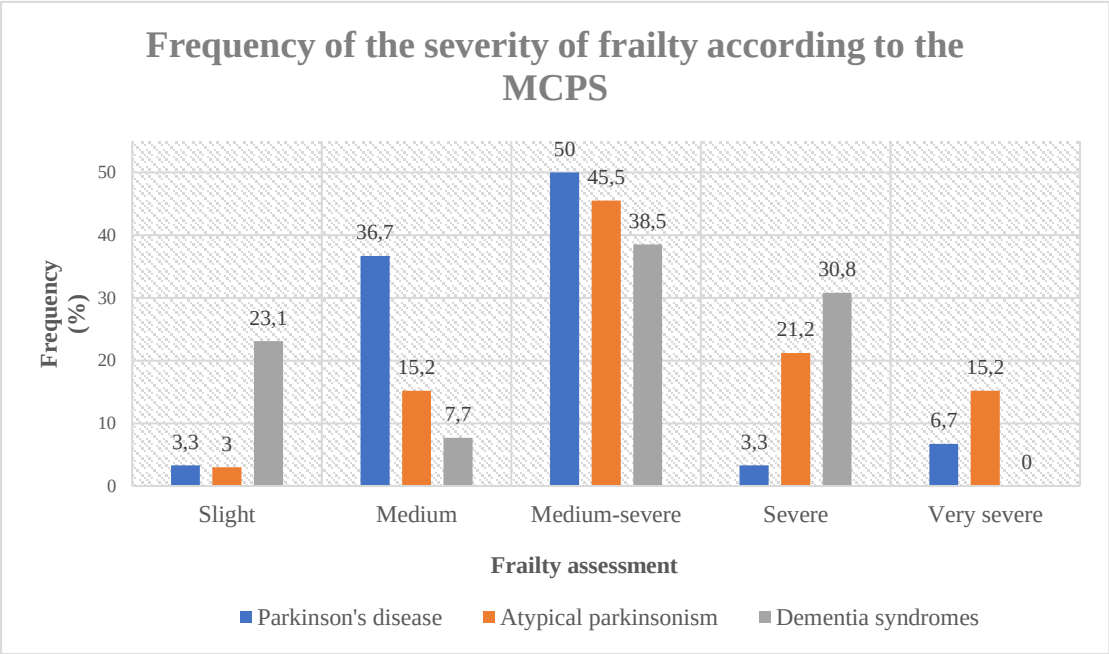

Figure 2. Frequency of the severity of frailty assessed by the Marigliano-Cacciafesta Polypathological Scale (MCPS) according to the neurodegenerative disorder (n=76).

The MCPS and the severity of parkinsonian syndromes showed a moderate correlation (r=0.451; p=0.000), while no correlation was found between MCPS and the severity of dementia (r= 0.321; p=0.285, respectively).

Nutritional status

According to the different nutritional parameters, the frequencies of undernutrition, risk of undernutrition, normal nutritional status and overweight or obesity are presented in figure 3.

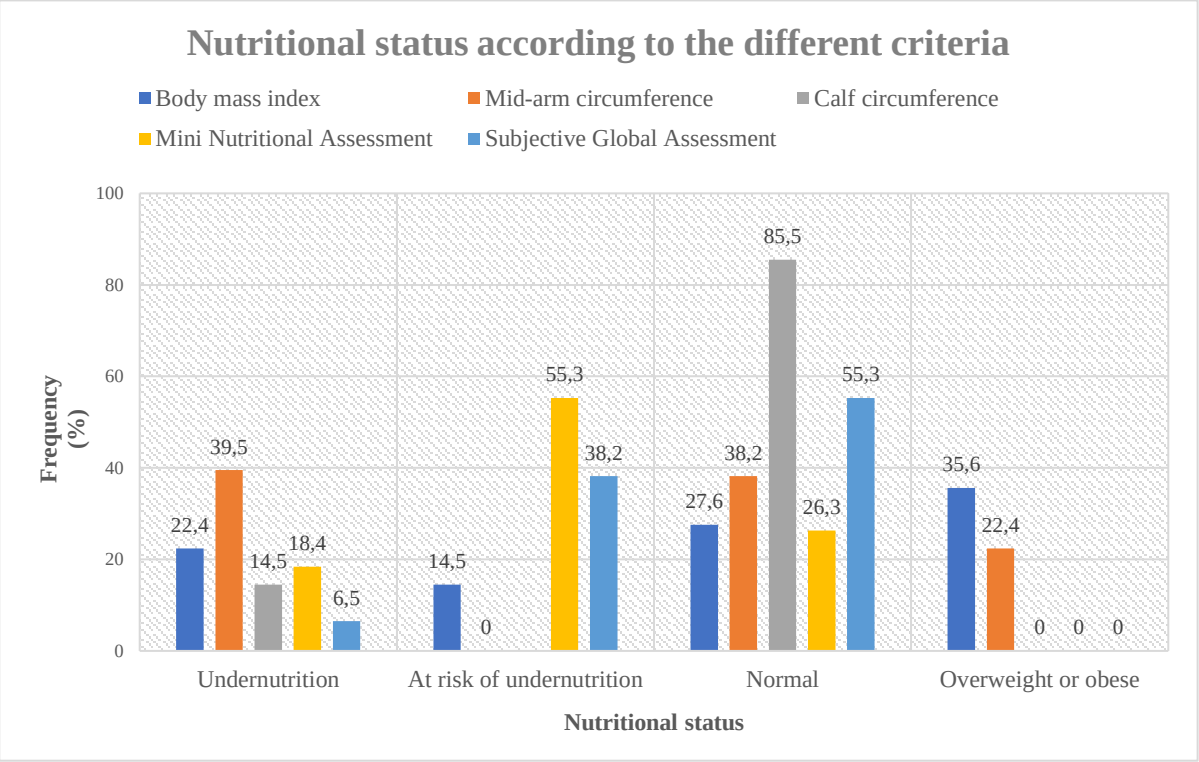

Figure 3. Nutritional status according to the different criteria in the moment of admission (n=76).

MNA

Although, in the admission moment, no statistically significant differences were found between parkinsonian and dementia syndromes regarding nutritional status assessed by the MNA (table 3), the dementia syndromes group seem to have a higher frequency of undernutrition (figure 4).

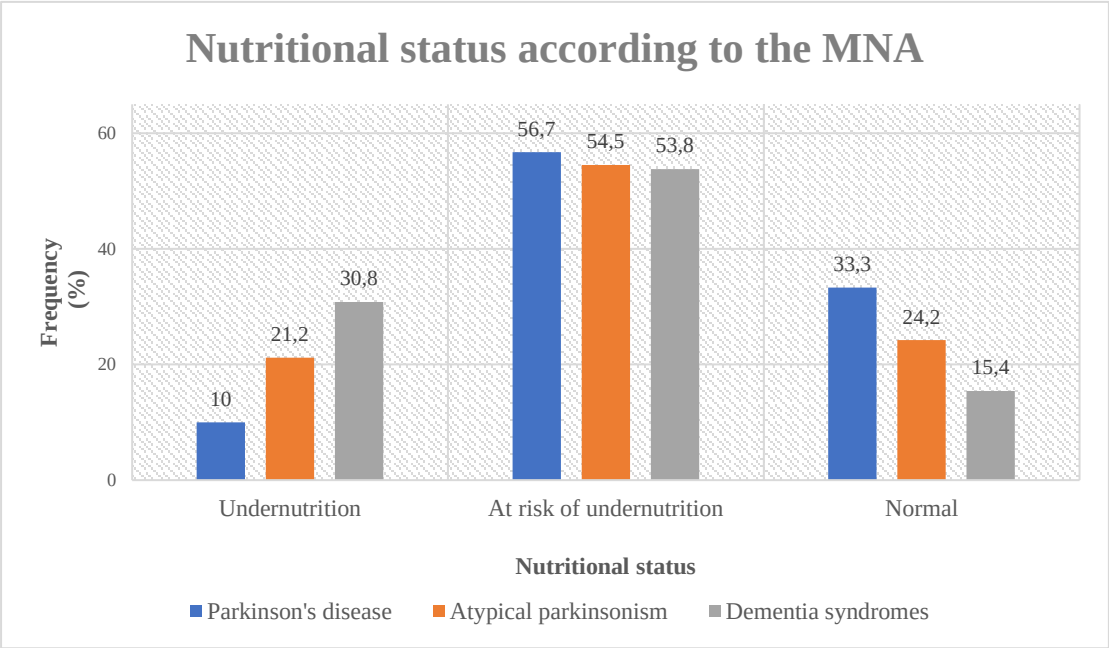

Figure 4. Frequency of nutritional status according to the Mini Nutritional Assessment (MNA) for the different neurodegenerative disorders (n=76).

BMI

Most of the patients with PD were obese (30%), while atypical parkinsonism were more frequently normal (30.3%) and dementia syndromes undernourished (23.1%) (figure 5).

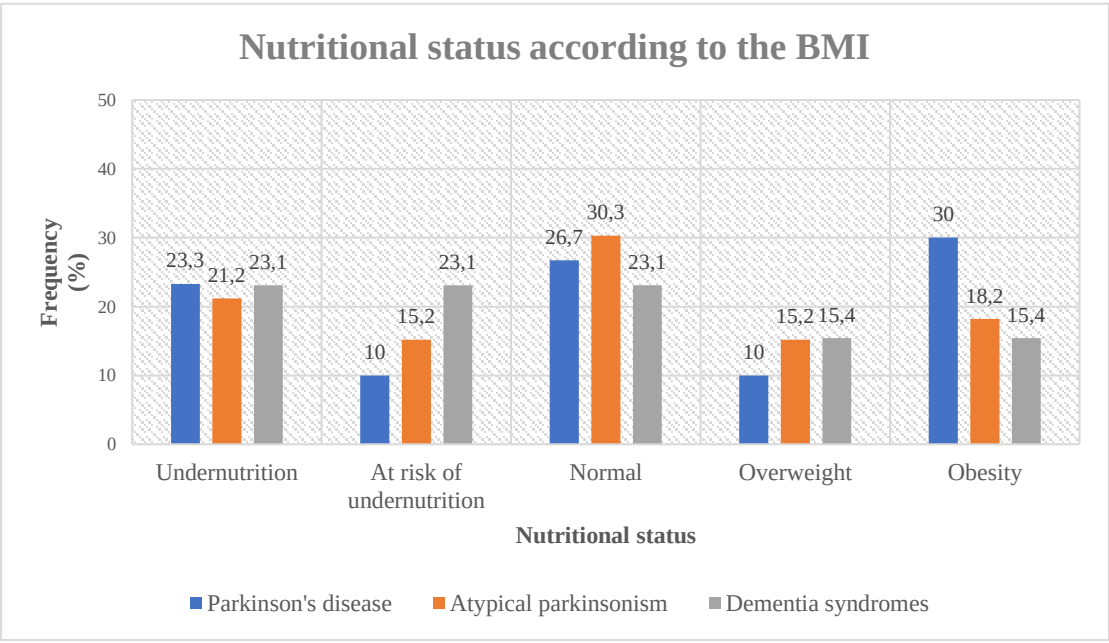

Figure 5. Frequency of nutritional status according to the body mass index (BMI) for the different neurodegenerative disorders (n=76).

Nutritional status and the severity of the neurodegenerative disease

Correlations between the severity of dementia syndromes, assessed by the CDR score, and nutritional status parameters were not found.

Regarding the severity of the parkinsonian syndromes, only the MNA (r= -0.394; p=0.001), the EdFED-Q (r=0.315; p=0.012) and the SGA (rs= -0.308; p=0.014) evidenced a significant, although weak, correlation with H&Y.

Frailty and Nutritional status

Significant correlations were found between the nutritional assessment parameters and the MCPS. The MNA and the EdFED-Q scores both showed a strong correlation with the MCPS (table 5).

	Body mass index	**MAC**	**CC**	**MNA**	**EdFED-Q**	**SGA**
MCPS	r= -0.363**	r= -0.347**	r= -0.477**	r= -0.732**	r= 0.714**	rs= -0.437**
CFS	rs=0.227*	rs=0.302**	rs=0.341**	rs=0.629**	rs= -0.689**	rs=0.507**

Table 5. Correlations between frailty scales and nutritional parameters.

MCPS (Marigliano-Cacciafesta Polypathological Scale), CFS (Clinical Frailty Scale), Mid-arm circumference (MAC), Calf circumference (CC), Mini Nutritional Assessment (MNA), EdFED-Q (Edinburgh Feeding Evaluation in Dementia Questionnaire), Subjective Global assessment (SGA).

* $p<0.05$ ** $p<0.01$

Statistically significant differences between reassessment moments were not found regarding the MCPS (figure 6).

Statistically significant differences between the score of the MNA in the admission moment and in the first reassessment moment were found only in parkinsonian syndromes (W= -2.524; p=0.012). Between the admission and the three-month reassessment no differences were found in the MNA score (figure 6).

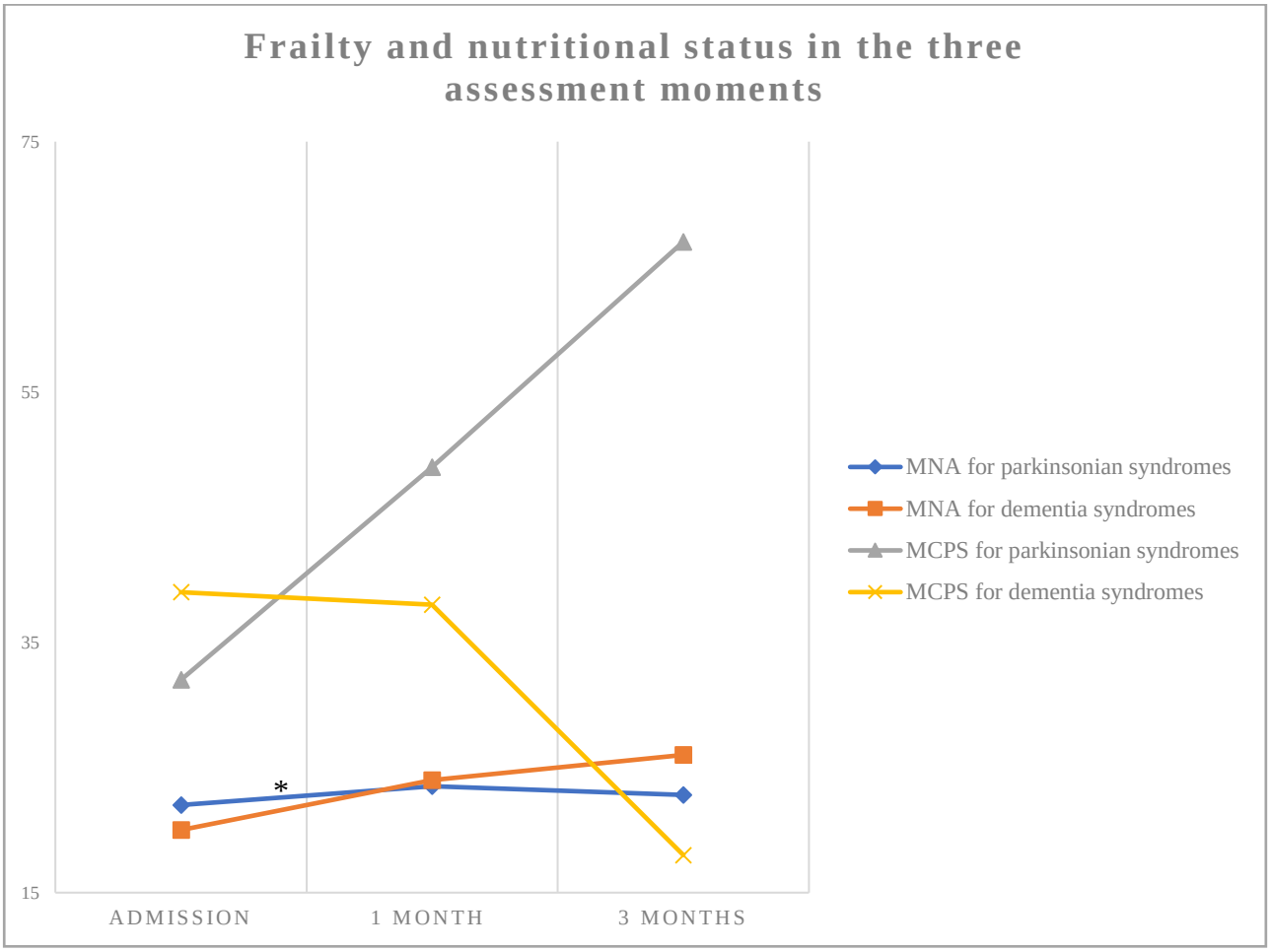

Figure 6. Comparison between frailty assessed by the Marigliano-Cacciafesta Polypathological Scale (MCPS) and nutritional status assessed by the Mini Nutritional Assessment (MNA) in the three assessment moments.
Wilcoxon test for paired samples * $p<0.05$

The relation between frailty and BMI in parkinsonian, atypical parkinsonism and dementia syndromes is described in figures 7 to 9.

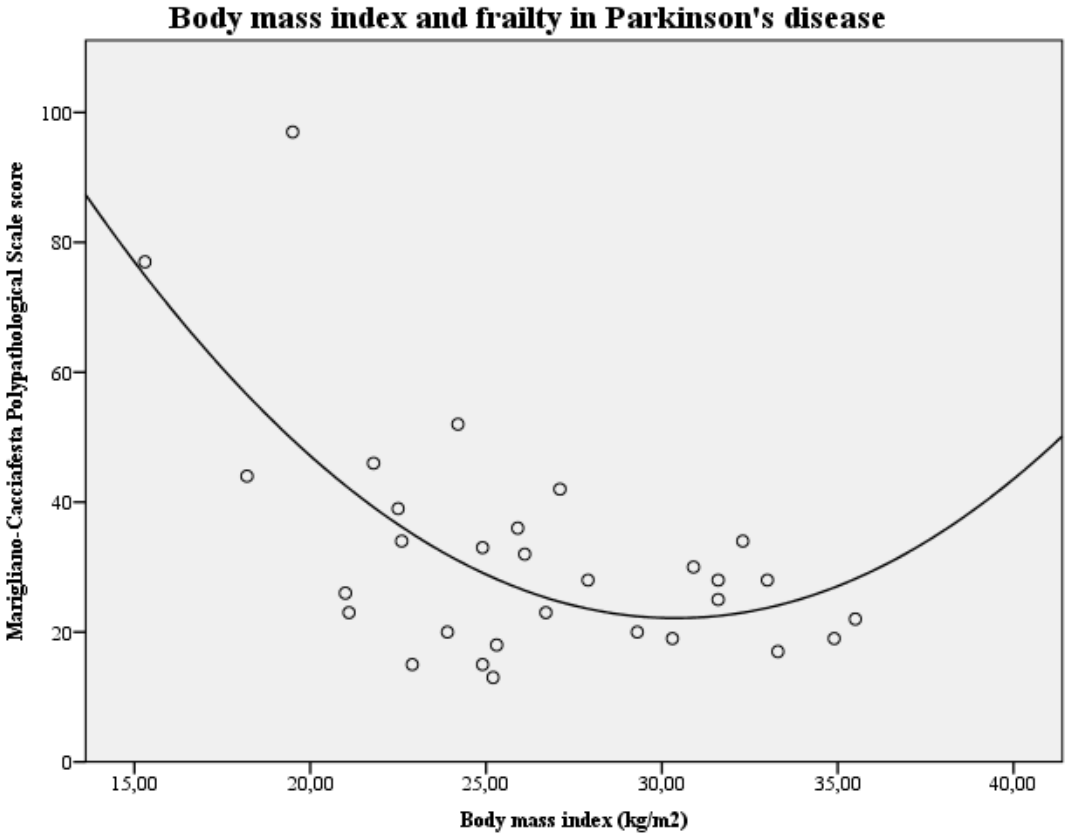

Figure 7. Relation between frailty and body mass index in parkinsonian syndromes.

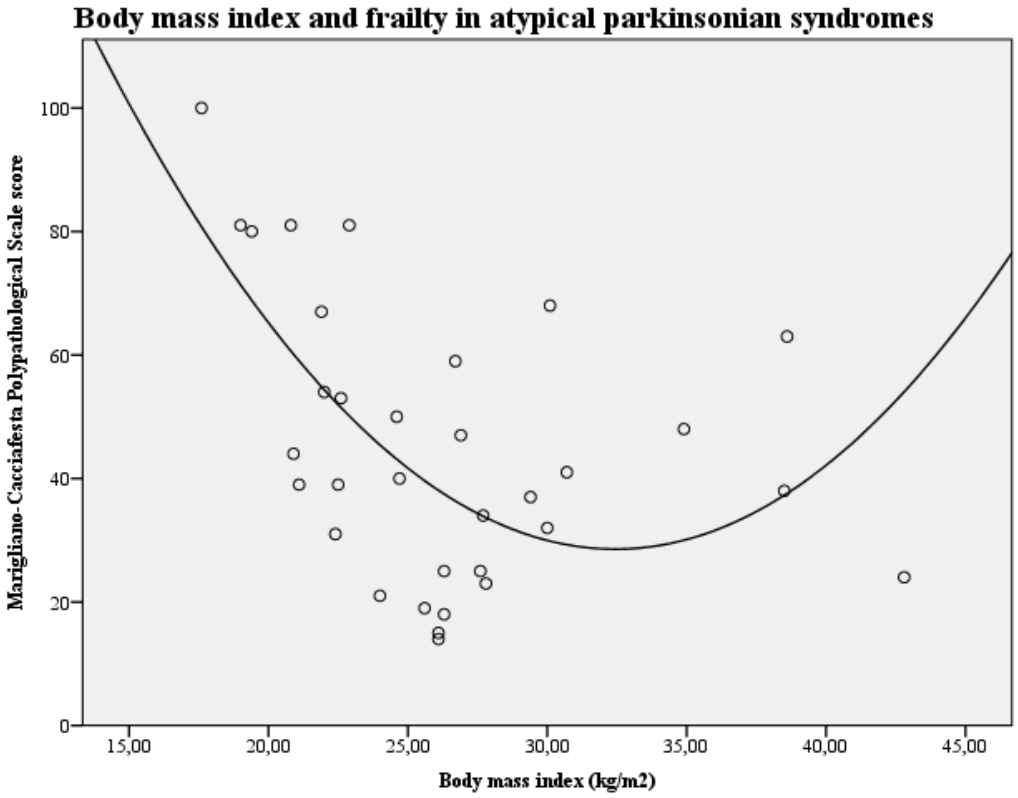

Figure 8. Relation between frailty and body mass index in atypical parkinsonian syndromes.

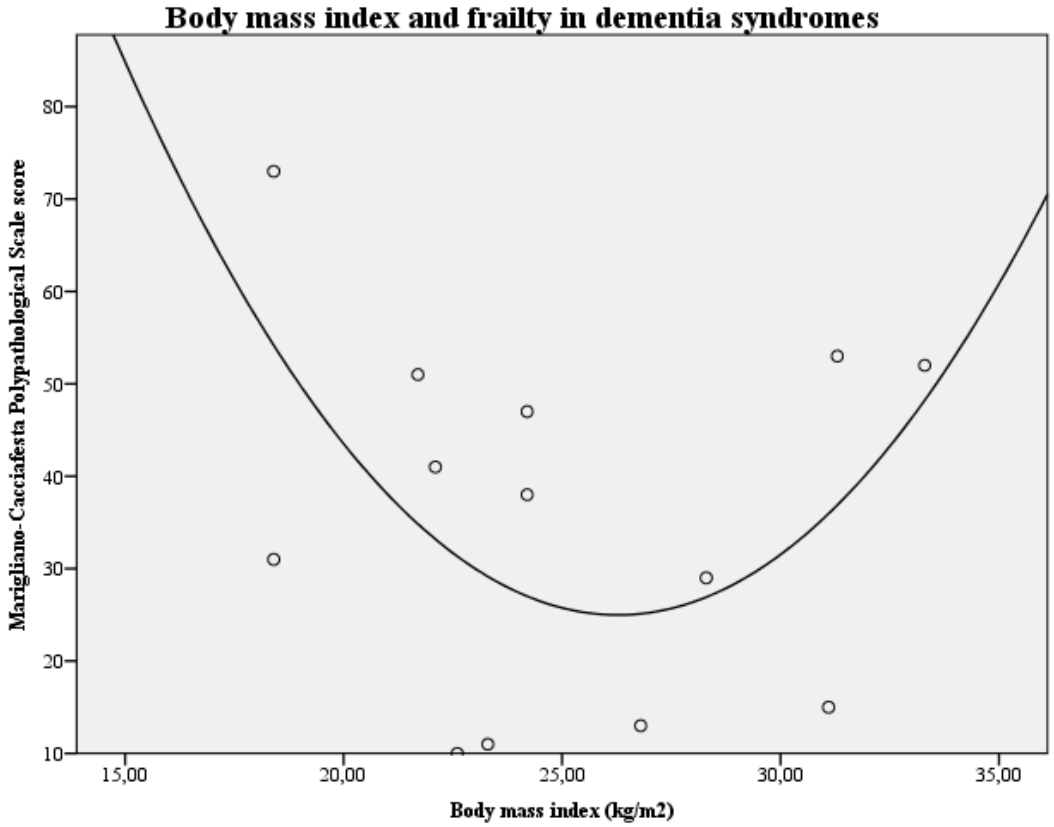

Figure 9. Relation between frailty and body mass index in dementia syndromes.

Discussion

Frailty

In the present study, the frequency of frailty in institutionalized patients with neurodegenerative disorders is high (71.1%).

Due to the lack of studies regarding frailty performed in institutionalized patients with neurodegenerative disorders, the comparison of our results was difficult[21]. However, the prevalence found in our study was considerably higher than in previous studies with community-dwelling older adults, since the overall prevalence of frailty in 10 European countries is 17%[19,69]. In Portugal, the prevalence of frailty, assessed by the PFP, is 35%, mostly in women and in advanced ages[146].

Evidence of the prevalence of frailty in nursing homes is scarce, possibly due to the limitations on the application of the screening tools, since most of them requires the physical or mental collaboration of the patient, that may be lacking in an institutionalization context. The high levels of dependence, comorbidity, disabilities, and malnutrition in the long-term care may contribute to this[21].

A systematic review published by Kojima and colleagues regarding 9 studies performed with institutionalized elders, estimated a prevalence of 52% frail elders and 40% prefrail according to different assessment criteria (PFP, CFS, Edmonton Frail Scale, and two others)[21]. In our institutionalized older adults sample (average age of 76±6.8 years), the frequency of frailty is considerable higher, and our sample is younger than the one found by the systematic review (80.3 years)[21]. This can evidence that even younger, the load of the neurodegenerative disorder can influence the risk and/or severity of frailty in this population. However, the clinical characteristics of the population pooled by the systematic review were not described[21].

Also, the higher frequency of frailty in our study when compared with other studies performed in nursing homes or long-term care institutions, may be related to the specific setting were data was collected – an institution specialized in neurodegenerative disorders. This means that the majority of the patients had a

neurodegenerative condition, which may not be necessarily true for general nursing homes that have a more heterogenous population regarding clinical diagnosis.

Although few studies using the MCPS are published, this tool has been considered useful for screening frailty and to programme an intervention/rehabilitation by its stratification of the severity of frailty[28,147].

We found that frailty was higher in the dementia group than in parkinsonian syndromes, although not statistically significative, independently of the assessment tool. However, we found that participants with atypical parkinsonism presented more severe frailty than PD, according to the MCPS. Also, the atypical parkinsonism participants presented more severe disease than PD. These differences are in concordance with the literature[148–152]. Atypical parkinsonism usually have a faster and more severe progression than PD, with a poor response to dopaminergic treatment, worse prognosis, shorter survival and more complications in early stages[145,152]. Motor features such as early postural instability and falls, early dysarthria and dysphagia, dystonia, and impaired response to levodopa treatment are frequent in atypical parkinsonism, along with early and severe cognitive and behavioural changes, apraxia, hallucinations, orthostatic hypotension, and urinary dysfunction[145].

In our study, the frequency of frailty in the moment of admission, in patients with parkinsonian syndromes in the admission moment was 70.6% (corresponds to the sum of medium-severe, severe and very severe frailty). Specifically, in PD the frequency was 60% and in atypical parkinsonism was 85.7%.

In a sample of 133 patients in an acute hospital with an average age of 74 years, the frequency of frailty was 75.9%, which is similar to our results although assessed with another assessment criteria[90]. Also, 76.7% of those patients were malnourished and at risk of malnutrition[90].

Although moderate, we found a statistically significant correlation between frailty and the severity of parkinsonian syndromes. A small number of studies had described the prevalence of frailty in PD, and some of them demonstrated that females with PD have a higher risk of frailty than males[46–48]. Also, the severity of PD assessed with the unified Parkinson's disease rating scale and levodopa dose, seem higher in frail patients[47,48].

The high frequency of frailty found in our study was expectedly high, since some of the clinical features of parkinsonian and dementia syndromes are considered major risk factors for frailty and are part of several assessment tools. Slow gait speed is a common feature of parkinsonian syndromes, along with postural instability, risk of falls and balance impairment[153–155]. Depression, cognitive decline, malnutrition, and urinary dysfunction may also occur especially in advance stages[156–158]. Since most of our participants were rated as high severity level of the neurodegenerative disease, this frequency seems reasonable.

Nutritional status

The frequency of undernutrition and the risk of undernutrition according to the MNA in our study is also high, and in concordance with a previous study performed in similar population (73.7 *versus* 77.1% respectively[72]), and, in general, higher than published studies in nursing homes or community[59,62,68–70,72,159,160].

Besides the wide variation, depending on the applied methodology, in PD patients the general prevalence of malnutrition varies between 0-24% while 3 to 60% are estimated to be at risk[64]. When assessed with the MNA, the variation between studies decreases to 0-2% of malnourished and 20-34% at risk[64]. Our results in PD patients regarding undernutrition and risk of undernutrition (66.7%) were similar to the ones obtained in a sample of 34 institutionalized PD elders, where 62% were malnourished or at risk at the admission according to the MNA[72].

Body weight and PD share a relation that is still unexplained[156]. Weight loss is frequent, especially in advanced stages of the disease, and it has been shown that weight loss and low body weight (and BMI) are associated with a higher risk of developing dyskinesia due to the higher ratio of levodopa dose per kilogram (>6mg/kg)[161]. Also, weight loss is associated with mortality and poor quality of life[71,161].

The frequency of undernutrition or risk of undernutrition in patients with LBD in our study (n=12) was 83.3%, which is higher than the one found by Roque and colleagues in a community setting (77.3%)[76].

Regarding dementia syndromes, 84.6% of the patients were undernourished or at risk according to the MNA. Specifically, in AD patients (n=5), 80% was undernourished or at risk of undernutrition. Despite the small number of patients with AD included, this frequency is higher than the one found in community-dwelling AD elders (varies from 14.1 to 55.9%)[76].

Frailty and Nutritional status

Interestingly, the general frequency of undernutrition (or risk of) is very similar to the frequency of frailty. This goes in favour of the strong correlation between MNA and MCPS that was demonstrated in our study ($r= -0.732$; $p<0.01$) and in line with previous studies regarding the correlation between nutritional status and frailty[69,90]. The MNA assesses several risk factors for frailty, namely weight loss and low BMI, reduced mobility, and low nutritional intake. In the parkinsonian syndromes, the undernourished participants were also the ones with more severe frailty while the patients at risk of undernutrition were also medium-severely frail. In dementia syndromes similar tendency was verified.

On the other hand, the correlation between BMI and MCPS was weak ($r= -0.363$; $p<0.01$). In the MCPS, nutritional status can be assessed with the MNA or the BMI, however the considered BMI cut-offs are commonly used for adults and not for elders. This means that an elder can be mistakenly considered overweight instead of normal since the reference value for normal in older adults is 24-26.9kg/m^2 that is close to overweight cut-offs in adults (25-29.9kg/m^2). Despite this, in our study we also found a U-shaped relation between frailty and BMI[78,79,83]. This relation was more obvious in parkinsonian syndromes than in dementia syndromes possibly due to the differences in the number of participants in both groups.

Since frailty is considered a dynamic state and reversible in some of its components, we performed a comparison between the admission moment and one-month after. Although the differences were not statistically significant, is evident that the severity of frailty tends to increase one month after the admission in the parkinsonian syndromes

group. Despite the low number of remaining patients to the reassessment, this may be related to the high severity of the disease in the admission, the lack of some clinical information that were only diagnosed after the first 48 hours of admission (and thus, not considered for the frailty assessment in the admission moment but only in the reassessment) such as the presence of hiper- or hypotension, and the unknown neurological diagnose (regarding patients that could be admitted for diagnostic investigation).

Parkinsonian syndromes are degenerative conditions that, especially in advanced stages or in atypical parkinsonisms, can have a faster progression, higher severity, and higher rates of physical dependence[76,145,152]. Also, the management of parkinsonian syndromes is difficult, especially in more advanced stages of the disease, and takes time for pharmacological treatment to be adjusted to achieve a balance of motor and/or non-motor control and functionality[162–164].

On the other hand, dementia syndromes tended to decrease the severity of frailty since the admission. Behaviour changes, food refusal and severe feeding difficulties are common in dementia patients, especially in more advanced stages[29,165]. In our study, feeding difficulties were more frequent in dementia than in parkinsonian syndromes in the admission moment, however in the one-month reassessment this frequency decreased in dementia syndromes along with the decreasing in the severity of frailty and improved nutritional status. Since the correlation between the MCPS, the MNA and the EdFED-Q is strong this may justify the improvement of frailty in this group in the reassessment moment.

In general, we can notice the institutionalization seems to contribute to improve the nutritional status of both parkinsonian and dementia syndromes. Regarding frailty, an increase on its severity in parkinsonian syndromes tends to appear despite of a slight improvement on nutritional status.

The timing to reassess these patients may had been short to see changes in frailty, due the complexity of these diseases and significant changes on some domains of the MCPS may take longer than one or three-months.

Limitations

Our study has some limitations. First, the low number of participants included in the reassessment moments. Second, the unbalanced proportion of participants with parkinsonian and dementia syndromes.

The initial research protocol previewed the application of the PFP criteria, however due to the level of collaboration needed to perform this assessment only a few number of participants would be able to complete it since most were in severe stages of the diseases. Also, the PFP validation study specifically excluded patients with the neurodegenerative disorders that we aimed studying[10].

The study of the clinimetric properties of the MCPS were predicted but not feasible due to the insufficient sample size[166].

As a tool for frailty assessment, the MCPS is, in our point of view, comprehensive in most of the described risk factors for frailty, objective, and stratifies the severity of frailty. Also, when compared with other tools, the MCPS has the advantage of not being dependent on the patients' collaboration to be fulfilled.

The MCPS is a complex multidomain tool to be applied by a single health professional meaning that a multidisciplinary filling would be preferable to more accurately assess frailty in all its domains.

On the other hand, the MCPS also has also some limitations. The scale, although comprehensive, lacks on some specifics. For instance, in the renal disorders section, 1 point should be attributed if the patient present rare episodes of urinary incontinence; however, if the patient have urinary incontinence there is no correspondent score. In this case, the investigators considered a 10-point score that corresponds to the next level of severity in this item. In the metabolism and nutritional state item, the MCPS adds, in comparison to other tools, the possibility to consider higher BMI as a severity component for frailty. However, the cut-off values for BMI are for adults and not specifically for elders over 65 years old. This can influence the results when trying to correlate the MCPS with BMI. Also, in some situations the investigator is confronted with patients with a normal MNA score (≥23.5 points) but a BMI of 26kg/m^2 that would

be considered by the scale as overweight. In this case, we must choose which parameters matters the most leading to subjectivity and possibly to inter-ratter's variability.

Based on our results, the MCPS could be a useful tool to assess and stratify the severity of frailty in institutionalized older adults. Future research should be performed to validate this tool and an analysis on which specific domains from the MCPS are the major contributors to frailty and which ones are changeable by intervention.

Conclusions

The frequency of frailty in institutionalized patients with neurodegenerative disorders is, as expected, high. Similar frequency of undernutrition (or risk of) was found. Nutritional status and frailty seem to be significantly correlated. Since inadequate nutrition and/or poor nutritional status are potentially treatable causes for frailty, it seems reasonable to further investigate the effects of therapeutic nutritional interventions to prevent and to treat frailty.

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Annexes

Annex I – Information sheet

Folha de Informação para os participantes

Título do projecto de investigação

Fragilidade e estado nutricional em utentes com doenças neurodegenerativas.

Objectivo do estudo

O objetivo principal do estudo é descrever a frequência da fragilidade em indivíduos com doenças neurodegenerativas na admissão de uma instituição de saúde. Os objetivos secundários são descrever a frequência da desnutrição, avaliar a correlação entre o estado nutricional e a fragilidade na admissão e comparar a frequência da desnutrição e fragilidade um a três meses após a institucionalização.

Procedimento

Na admissão da instituição, será avaliada a fragilidade (através de 3 escalas) e o estado nutricional (através de medições antropométricas e 2 escalas). Se possível, 1 a 3 meses após a admissão serão reaplicados os mesmos procedimentos para comparação.

Possíveis benefícios para os participantes

Se concordar em participar, não terá nenhum benefício clínico direto. Contudo, a sua participação poderá contribuir para o aumento do conhecimento sobre a fragilidade e estado nutricional de utentes com doenças neurodegenerativas, o que poderá beneficiar os doentes ou terceiros no futuro. Não receberá nenhuma compensação económica pela sua participação neste estudo.

Riscos físicos previsíveis

Não está previsto qualquer risco decorrente da participação neste estudo.

Participação voluntária e direitos de abandono

Se concordar em participar, a qualquer momento pode desistir e solicitar que os dados recolhidos neste estudo sejam eliminados sem qualquer consequência para si.

Utilização dos dados

Se assinar este consentimento, dará permissão ao investigador principal envolvido neste estudo, bem como aos seus orientadores, para que utilizem informações demográficas, adequadamente

anonimizadas. A informação usada neste estudo, e que poderá ser divulgada, inclui dados que serão anonimizados, de forma a que não seja possível associar a identidade às avaliações e aos dados demográficos. A futura apresentação e publicação dos resultados do estudo respeitará sempre a confidencialidade dos dados e o anonimato dos participantes.

Contatos

Poderá contactar a investigadora principal do estudo, Mestranda Diana Miranda para responder a qualquer dúvida que tenha relativamente ao estudo e à sua participação no mesmo.

Contacto telefónico: 917 151 826

Email: diana.santos.miranda@gmail.com

Annex II – Informed consent

Fragilidade e estado nutricional em indivíduos com doenças neurodegenerativas

Informação aos participantes

A fragilidade é uma síndrome caracterizada por um estado de vulnerabilidade aumentada a qualquer mudança ou acontecimento mínimo de *stress*, que pode contribuir para o comprometimento da independência e qualidade de vida dos doentes. O estado nutricional parece ter um papel importante no desenvolvimento da fragilidade.

A pertinência do estudo que propomos prende-se com o esclarecimento da frequência da fragilidade e relação entre a fragilidade e o estado nutricional em indivíduos com doenças neurodegenerativas.

Ao aceitar participar, serão preenchidas três escalas de avaliação da fragilidade e duas escalas de avaliação do estado nutricional. Adicionalmente serão recolhidos e registados o peso, altura, perímetro da perna e perímetro do braço. Estes dados serão recolhidos na admissão, um mês e três meses após a admissão.

Todos os dados sociodemográficos e clínicos colhidos serão armazenados de forma codificada, de modo a proteger os seus dados pessoais. Em nenhuma ocasião, o seu nome figurará nos documentos finais de estudos ou em publicações científicas dos resultados.

Caso decida não participar, quer antes de iniciar os procedimentos do estudo, quer a meio, não será prejudicado. Para tal, basta comunicar-nos a sua decisão e todos os seus dados pessoais que tenham sido recolhidos serão apagados de forma definitiva.

Agradecemos desde já a sua colaboração e vontade em participar.

Consentimento informado

Eu, abaixo assinado, aceito participar no estudo intitulado “Fragilidade e estado nutricional em indivíduos com doenças neurodegenerativas”

Nome completo _____

Data _____

Assinatura _____

*No caso de participantes com compreensão comprometida

Responsável Legal* _____

Testemunha* _____

A preencher pelo investigador que fornece o consentimento informado:

Data_____ Instituição _____

Assinatura_____

Fragilidade e estado nutricional em indivíduos com doenças neurodegenerativas

Consentimento informado para o centro de investigação

Eu, abaixo assinado, aceito participar no estudo intitulado "Fragilidade e estado nutricional em indivíduos com doenças neurodegenerativas"

Nome completo _____

Data _____

Assinatura _____

*No caso de participantes com compreensão comprometida

Responsável Legal* Nome _____

Assinatura _____

Testemunha* Nome _____

Assinatura_____

A preencher pelo investigador que fornece o consentimento informado:

Data_____ Instituição _____

Assinatura_____

Annex III – Case report form

Frailty and nutritional status in patients with neurodegenerative disorders - CRF

Subject ID (CNS number):

Date of admission: ___/___/_____ Date of assessment: ____/____/_____

A) General features

- Age, years: Gender:
- Weight, kg: Height, cm:
- Main neurodegenerative disorder: _____
- Medical history clinical background: _____

  _____

  _____
- If PD patients, Hoehn & Yahr:
- If dementia patients, CDR:

B) Outcome assessment scales

1) Nutritional Assessment

1.1) Mini Nutritional Assessment Full-Form (MNA-FF) score:

1.2) Subjective Global Assessment (SGA) score:

1.3) Body Mass Index (kg/m^2): _____ (Classification: _____)

1.4) Calf circumference (cm): _____

1.5) Mid-arm circumference (cm): _____ (1988-1994 CDC percentile: _____)

1.3) Edinburgh Feeding Evaluation in Dementia Questionnaires (EdFED-Q)

A) O doente necessita de supervisão próxima durante a refeição?
0 = Nunca
1 = Às vezes
2 = Frequentemente

B) O doente necessita de apoio físico para a realização da refeição?
0 = Nunca
1 = Às vezes
2 = Frequentemente

C) Existe derrame durante a refeição?
0 = Nunca
1 = Às vezes
2 = Frequentemente

D) O doente tende a deixar comida no prato no final da refeição?
0 = Nunca
1 = Às vezes
2 = Frequentemente

E) Alguma vez o doente recusa alimentar-se?
0 = Nunca
1 = Às vezes
2 = Frequentemente

F) O doente vira a cara enquanto está a ser alimentado?
0 = Nunca
1 = Às vezes
2 = Frequentemente

G) O doente recusa-se a abrir a boca?
0 = Nunca
1 = Às vezes
2 = Frequentemente

H) O doente cospe a comida?
0 = Nunca
1 = Às vezes
2 = Frequentemente

I) O doente permanece de boca aberta permitindo que a comida caia?
0 = Nunca
1 = Às vezes
2 = Frequentemente

J) O doente recusa-se a engolir?
0 = Nunca
1 = Às vezes
2 = Frequentemente

Total Score: _____

2) Frailty

2.1) The Marigliano-Cacciafesta polypathological scale

1. Neurological disorders	
Absence of disorder	0 point
Multi-infarct encephalopathy detected by instrumental examinations in the absence of evident symptoms	1 point
Previous strokes without remaining effects or with effects disappearing after rehabilitation/initial Parkinson's disease	5 points
Previous strokes with slight remaining effects/Parkinson's disease being treated with L-Dopa	8 points
Previous stroke with paralysis/Parkinson's disease in an advanced stage not controlled with pharmaceutical treatment/previous cranial trauma with remaining effects and/or post-traumatic epilepsy	25 points
2. Cardiopathy	
Absence of disorder	0 point
NYHA 1: asymptomaticity, with only signs detectable by instruments (ECG or echocardiography) and/or minimal objective signs (e.g., slight puffing)	1 point
NYHA 2: dyspnea induced by everyday activities (flight of stairs, block of flats), slight-moderate edemas, conditions controlled by treatment	5 points
NYHA 3: dyspnea induced by activities less strenuous than everyday, emphatic edemas, condition hardly controlled by treatment	8 points
NYHA 4: dyspnea when resting	25 points
3. Respiratory disorders	
Absence of disorder	0 point
Asymptomaticity, only thoracic objectivity or X-ray	1 point
Chronic coughing, dyspnea induced by everyday activities	5 points
Coughing phlegm in morning, dyspnea induced by activities less strenuous than everyday or when resting	10 points
Overall respiratory insufficiency (hypoxemia < 60 mmHg, hypercapnia > 50 mmHg)	25 points
4. Renal disorders	
Absence of disorder	0 points
Asymptomaticity with history of nephropathy or IVU, rare episodes of urinary incontinence, creatine <1.5 mg/dl	1 point
Non-complicated nephropathy creatine (<2.5 mg/dl), permanent catheterization	10 points
Dialysis, terminal uremia	25 points
5. Locomotive apparatus disorders	
Absence of disorder	0 point
Occasional pain	1 point
X-ray compatible with degenerative or inflammatory arthropathy	2 points
Continuous osteoarthritic pain, joint mobility slightly moderately compromised	4 points
Continuous osteoarthritic pain and significant limitation of joint movement, not controllable with treatment, severe deformities, multiple vertebral collapses	15 points
6. Sensory deprivation (sight and hearing)	
Absence of impairment	0 point
Slight	4 points
Moderate, but with the use of corrective aids	6 points
Moderate	10 points
Severe	25 points
7. Metabolism and nutritional state	
Normal	0 point
Slightly compromised: MNA 17–23/overweight (BMI = 25–29.9)	1 point
Moderately compromised: MNA <17 and alterations of other indices/slight obesity (BMI = 30–34.9) or severe (BMI = 35–39.9)	4 points
Severely compromised: MNA <17, anemia, secondary decline/severe obesity (BMI ≥ 40)	15 points
Diabetes mellitus decompensation and/or with complications, severe malnutrition, bedridden syndrome	25 points

8. Cognitive state and mood	
Absence of disorder (clinical diagnosis and/or with tests: GDS, MMSE, . . .)	0 point
Compromised cognition and/or slight-euthymic depression after treatment/frequent social anxiety-discomfort (at least one episode per month) with occasional use of tranquillizers	1 point
Compromised cognition and/or moderate depression/frequent anxiety (more than two episodes per month) with need for stable treatment with tranquillizers	4 point
Compromised cognition and/or severe depression with greater need for treatment with tranquillizers	10 points
Dementia and/or major depression with psychosis needing pharmaceutical treatment	20 points
9. Peripheral vascular system	
Absence of disorder	0 point
Varicose veins	1 point
Phlebitis and/or recurrent ulcers	2 points
Intermittent claudication	4 points
Pulse at extremities lacking, gangrene and/or amputation of leg	10 points
10. Malignant cancerous disorders	
Absent	0 point
Local carcinoma	1 point
Locally advanced disease with surgery recommended (also in association with chemotherapy) and possible recovery	5 points
Locally advanced disease with surgery not recommended (lymphomas and chronic leukemia/myelodisplastic anemia)	15 points
Disease spread in terminal metastatic stage with cachectic state/lymphomas and acute leukemia	25 points
11. Gastroenteritic disorders	
Absence of disorder	0 point
Episodic disturbances	1 point
Constant symptoms present with signs that can be picked up by instruments and/or stable pharmaceutical treatment/correlated hepatopathy viruses	2 points
Chronic pathology without cure by pharmaceutical therapy and/or surgery	4 points
Hepatic insufficiency	25 points

Total score:

Slight polypathology <15 scores	
Medium polypathology 15-24 scores	
Medium-severe polypathology 25–49 scores	
Severe polypathology 50–74 scores	
Very severe polypathology >75 scores	

2.2) Clinical Frailty Scale

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 Managing Well – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with **all outside activities** and with **keeping house.** Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Score: _____

2.3) Physical Frailty Phenotype (Fried)

Critérios fenotípicos	Sexo masculino	Sexo feminino
1. Perda ponderal não intencional de 4,5kg ou >5% do peso corporal no período de um ano		
2. Avaliação do tempo de marcha de 4,6 metros (de acordo com altura)	> 1,73 cm - > 6 segundos < 1,73 cm - > 7 segundos	> 1,59cm - >6 segundos < 1,59cm - >7 segundos
3. Força de preensão avaliada por dinamómetro (de acordo com IMC)	IMC ≤ 24 - ≤29 IMC 24,1 - 26 - ≤30 IMC 26,1 - 28 <30 IMC ≥ 28 - ≤32	IMC ≤ 23 - ≤ 17 IMC 23,1 - 26 - ≤ 17,3 IMC 26,1 - 29 - ≤ 18 IMC ≥ 29 - ≤ 21
4. Diminuição da atividade física (Questionário de Atividades de Lazer de Minnesota ou consumo semanal quilocarias)	<383 kcal/semana	<270 kcal/semana
5. Exaustão avaliada por uma pontuação de 2 ou 3 no Questionário CES-D (Escala de Depressão do Centro de Estudos Epidemiológicos), devendo-se ler no item "Exaustão" as duas frases "Senti que tudo o que fazia era um esforço" e "Não conseguia ter força" e se deve responder à pergunta "Quantas vezes se sentiu assim na última semana?" – pontuando 0 raramente, 1 por vezes (1 a 2 dias), 2 moderadamente (3 a 4 dias), 3 grande parte do tempo.		